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SURGERY

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SURGERY

VOL. 28 OCTOBER, 1950 No. 4

Original Communications

CHLOROMYCETIN AND AUREOMYCIN IN EXPERIMENTAL GAS GANGRENE

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CINCINNATI, OHIO

(From the Department of Surgery of the University of Cincinnati College of Medicine and Cincinnati General Hospital)

THE prevention and successful management of gas gangrene and other clostridial infections have been greatly improved by the use of modern antibiotic agents in conjunction with early and adequate surgery. Our previous experimental work[1] showed that penicillin was particularly effective in controlling the spread of severe *Clostridium welchii* infection in animals, and similar experiments with bacitracin[2, 3] indicated that this agent also possessed marked therapeutic possibilities, although the renal irritation produced by larger doses limited its therapeutic usefulness. These results have been substantiated repeatedly in our clinical experience in the treatment of actual cases of gas gangrene by penicillin used in conjunction with the indicated surgery.

Soon after their introduction, the new chemotherapeutic agents, first Chloromycetin and later aureomycin, were studied to determine their possible usefulness and limitations in the treatment of experimental gas gangrene. Preliminary studies were made of their antibacterial effect in vitro for 8 strains of *Cl. welchii*, 7 of which were obtained through the courtesy of the Anaerobic Subcommittee of the British Research Council from actual cases of gas gangrene developing in battle casualties during the African campaign of World War II. The other strain, BP6K, is one whose high virulence has been well established by us in previous experiments carried out under the auspices of the National Research Council and United States Army during the past 5 years.[1, 4, 5] The results of these in vitro tests indicated that 5 of the 8 strains were susceptible to the action of Chloromycetin while all 8 were even more susceptible to that of aureomycin in the test tube.

Animal experimentation was then undertaken to test the chemotherapeutic activity of Chloromycetin and aureomycin in vivo for gas gangrene.

This paper is based on work done under a grant from the United States Army, Office of the Surgeon General.

Read before the Thirteenth Clinical Congress of the International Society of Surgery, New Orleans, La., Nov. 14, 1949.

Received for publication, Dec. 5, 1949.

TABLE I. IN VITRO SUSCEPTIBILITY OF EIGHT STRAINS OF VIRULENT CL. WELCHII

STRAIN	SOURCE	VIRULENCE AS MLD* FOR PIGS	SUSCEPTIBILITY TO CHLOROMYCETIN	SUSCEPTIBILITY TO AUREOMYCIN
BP6K	Dr. Logan	.5 c.c. 10^{-7}	1.25 u/c.c.	0.039 u/c.c.
A180C	War Wound	.5 c.c. 10^{-5}	10 u/c.c.	0.09 u/c.c.
G6002	War Wound	.5 c.c. 10^{-8}	20 u/c.c.	0.625 u/c.c.
A247B	War Wound	.5 c.c. 10^{-5}	5.0 u/c.c.	0.00975 u/c.c.
G2106	War Wound	.5 c.c. 10^{-9}	1.25 u/c.c.	0.0195 u/c.c.
F5026	War Wound	.5 c.c 10^{-10}	0.3125 u/c.c.	0.03906 u/c.c.
A250	War Wound	.5 c.c. 10^{-8}	0.3125 u/c.c.	0.0195 u/c.c.
A181B	War Wound	.5 c.c. 10^{-7}	0.625 u/c.c.	0.0195 u/c.c.

*MLD—minimum lethal dose.

MATERIAL AND METHODS

Guinea pigs weighing 350 to 450 Gm. each were chosen as the experimental animals because of their pronounced susceptibility to infection with *Cl. welchii* and because of our knowledge of their behavior to this infection gained in previous studies.[1, 2, 4, 5] As in previous studies, the experimental infection was produced by the postoperative injection of carefully measured amounts of one or more minimum lethal doses of *Cl. welchii* into closed wounds containing crushed muscle and sterilized dirt similar to that originally used by Caldwell of New Orleans and Reed and Orr of Canada. Time will not permit its description here.

In each experiment the animals were divided into 2 or 3 groups of approximately 15 guinea pigs each. In addition to the control group, a second group was used for measurement of the prophylactic value of the chemotherapeutic agent in a given dose, and the third for determination of its therapeutic value when treatment was delayed for 4 to 8 hours after the inoculation of the bacteria, permitting the infection to become well established. A series of 12 experiments, each involving 30 to 50 guinea pigs, was then carried out, 9 with Chloromycetin and 3 with aureomycin. A total of 470 animals were used, 120 being treated with Chloromycetin and 45 with aureomycin immediately after bacterial inoculation, 130 with Chloromycetin and 30 with aureomycin after a delay of 4 to 8 hours, and 145 being used as untreated controls.

Chloromycetin and aureomycin were given intramuscularly every 8 or 12 hours for a period of 96 hours in the earlier experiments, and every 8 hours for only 48 to 72 hours in subsequent experiments. Because of Chloromycetin's relative insolubility in any liquid except the glycols, it was administered in 20 to 50 per cent polyethylene glycol in the earlier experiments and in propylene glycol in the later studies. Aureomycin was given in leucine solution which was sterile when received.

The parenteral dose of Chloromycetin used varied between 10 and 150 mg. per kilogram per day, while that of aureomycin was 10 and 20 mg. per kilogram per day. In the immediate treatment group, the 24 hour dose of Chloromycetin per kilogram was 25 mg. for 60 animals, 50 mg. for 30 animals, 100 mg. for 20 animals, and 10 mg. for 10 animals. In the delayed therapy group, the 24 hour dose of Chloromycetin per kilogram was 25 mg. for 10 animals, 50 mg. for 40 animals, 100 mg. for 40 animals, and 150 mg. for 40

animals. The dose of aureomycin on the same basis was 10 mg. for 20 guinea pigs and 20 mg. for 25 guinea pigs in the immediate treatment group. For the delayed therapy group, it was 20 mg. in each instance. No further operative procedure or any other form of treatment was used and the animals and their wounds were then carefully observed and the date of death recorded in each instance. In this manner, it was possible to measure the effectiveness of either of the chemotherapeutic agents for a severe form of experimental gas gangrene closely resembling the human clinical type.

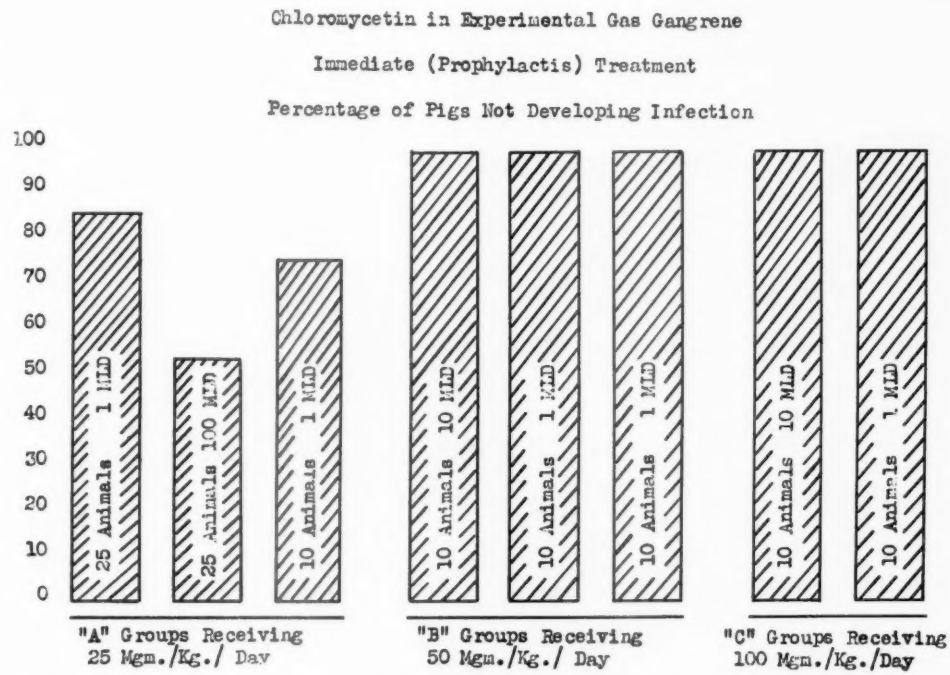


Fig. 1.—Graph showing the effectiveness of doses of 25, 50, and 100 mg. per kilogram per day in preventing the development of experimental gas gangrene when given intramuscularly immediately after inoculation of 1 to 100 minimum lethal doses of virulent bacteria. Control animals receiving the same inoculation all died within 72 hours of fulminating infection.

RESULTS

Chloromycetin—Immediate Treatment.—The results of immediate treatment with Chloromycetin varied with the number of minimum lethal doses of *Cl. welchii* injected and the dose of Chloromycetin used. Of the animals treated with 25 mg. per kilogram per day immediately after inoculation with 1 minimum lethal dose of *Cl. welchii,* 80 per cent of one group of 25 animals and 70 per cent of another of 10 animals did not develop grossly visible signs of infection, the other 20 and 30 per cent respectively developing definite but localized signs of gas gangrene (Fig. 1). In a third group of 25 animals receiving 100 minimum lethal doses, only 50 per cent of the animals did not develop signs of infection. In a fourth group of 15 animals treated with 10 mg. of Chloromycetin, only 20 per cent of the animals developed signs of infection and these were minimal. None of the animals showed an appreciable reaction at the site

of infection and in no instance was local tissue necrosis observed. However, the control animals receiving the same culture dilutions as the treated pigs were all dead within 72 hours and each demonstrated a massive infection with extensive gangrene.

Of the animals treated immediately with doses of 50 or 100 mg. of Chloromycetin per kilogram per day, none developed signs of gas gangrene after challenge with either 1 or 10 minimum lethal doses (Fig. 1). In most instances the local reaction in the region of the wound was no more than one would anticipate from the trauma and embedded foreign body dirt in the wound.

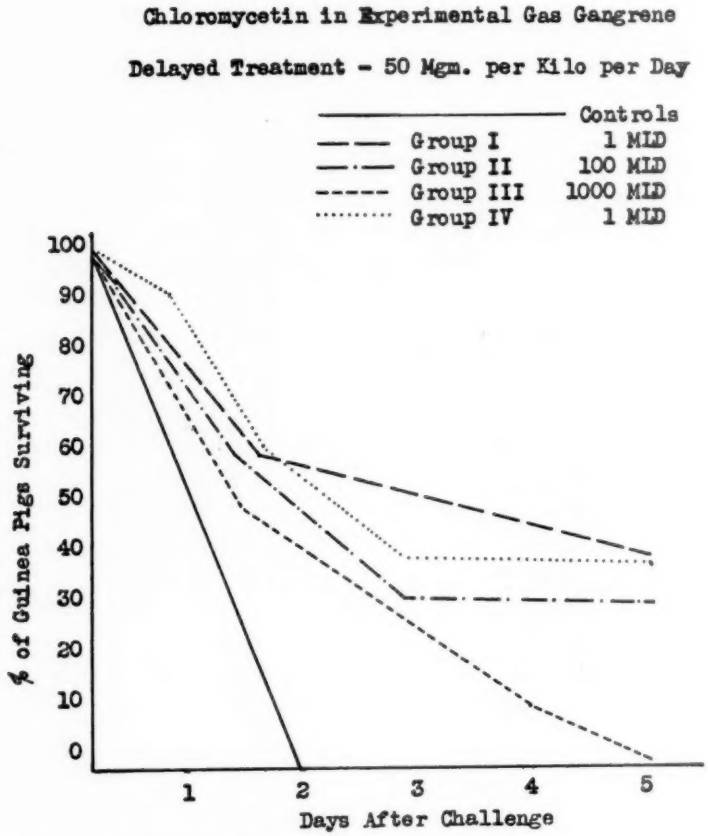


Fig. 2.—Graph showing the rate of death of 4 groups of guinea pigs dying with infection after treatment with 50 mg. of Chloromycetin per kilogram per day. Treatment began 4 hours after infection of animal.

The presence of gas was never detected and the minimal swelling diminished each day of survival. Again, the control animals receiving the same culture dilution rapidly developed overwhelming infection with much gas, swelling, discoloration, and gangrene.

Although the absence of infection was striking, many of these animals receiving Chloromycetin in glycol solution died either during the later phases of treatment or in the week after its cessation. A progressive impairment of activity and abnormal behavior became evident within 48 to 72 hours after the

initiation of therapy, and a rapidly degenerating nutritional status developed which was followed by an incidence of death in approximately 25 per cent of the animals.

The number of animals dying with toxic manifestations but without evidence of gas gangrene varied considerably in different experiments from 0 to 60 per cent, the average being 25 per cent. The incidence of toxic deaths varied with the type and dose of glycol, but not with the dose of Chloromycetin used. In some of the groups receiving 100 mg. per kilogram per day there were no deaths, while in others receiving 25 mg. on the same basis as many as 50 per cent died in this manner. In the fourth group of animals in which only 20 per cent propylene glycol solution was used for the administration of Chloromycetin, these toxic manifestations did not occur.

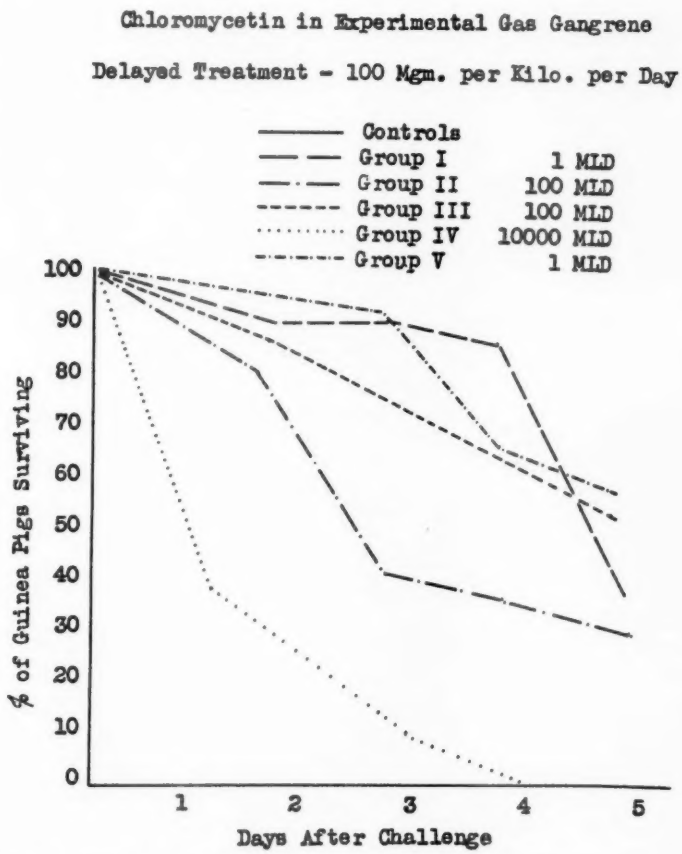


Fig. 3.—The therapeutic effect of Chloromycetin in controlling established experimental gas gangrene produced by 100 and 10,000 minimum lethal doses of *Cl. welchii*. This effect diminished as the number of minimum lethal doses used increased.

Although preliminary experiments with a single intramuscular dose of 2 c.c. of propylene and polyethylene glycol without Chloromycetin had shown no evidence of toxicity, the occurrence of unexplainable toxic manifestations and deaths in approximately 25 per cent of the animals treated by Chloromycetin-glycol mixtures caused us to investigate the toxicity of some of the

glycols further. Inoculations of 1 c.c. of propylene glycol every 12 hours for 4 days were followed by death of 20 per cent of the animals. Similar injections with polyethylene glycol caused the death of 70 per cent of the guinea pigs, and those with polypropylene glycol produced death in all of the animals. These studies demonstrate the toxicity of the glycols.

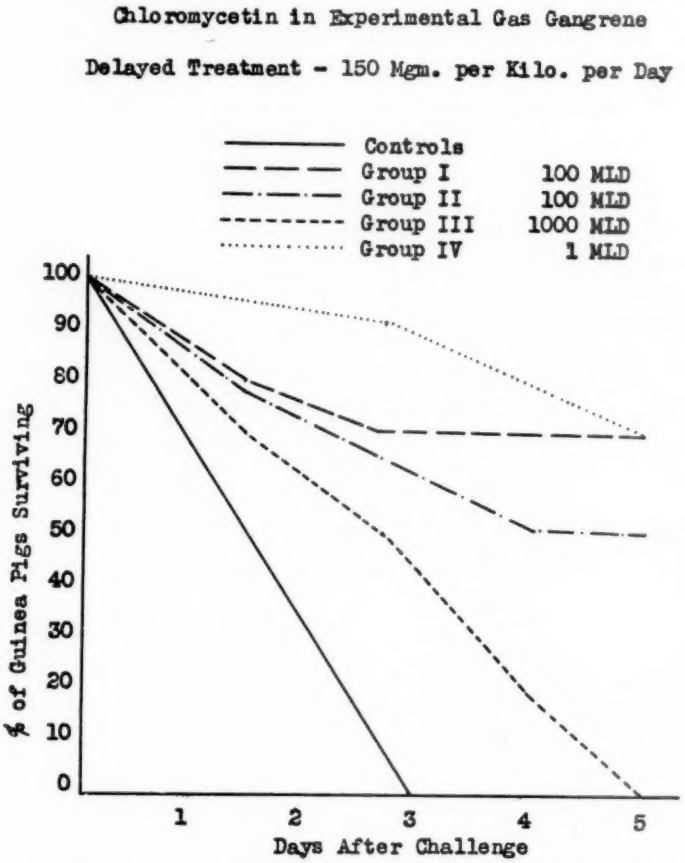


Fig. 4.—Similar chemotherapeutic effect of 150 mg. per kilogram per day in experimental gas gangrene. The difference in effect produced by 100 and 150 mg. per kilogram per day is not significant.

Chloromycetin—Delayed Treatment.—Both the incidence of gas gangrene and death from this lesion were much greater in all groups of guinea pigs treated with Chloromycetin after a delay of 4 or more hours (Figs. 2, 3, and 4). Unmistakable evidence of infection consisting of swelling, redness, and occasionally gas was already present at the time therapy was begun. However, the spread of the infection produced by 1 minimum lethal dose of *Cl. welchii* was obviously inhibited by the Chloromycetin, and 40 per cent of the animals treated with 50 mg. per kilogram per day survived (Fig. 2), 60 per cent of those treated with 100 mg. survived (Fig. 3), and 70 per cent of those treated with 150 mg. remained alive. All of the animals in control groups died of massive infection within 42 to 72 hours.

The animals which were treated therapeutically with Chloromycetin showed lesions which were less in area, swelling, production of gas, and discol-

oration than those of the untreated or control animals of the same day. Few survived if definite gas was demonstrable before the initiation of treatment.

Aureomycin—Immediate Treatment.—None of the animals treated with either 10 or 20 mg. of aureomycin per kilogram per 24 hours in 3 divided doses for 3 days developed any visible evidences of infection except slight swelling in the immediate vicinity of the wound. This receded spontaneously within 3 or 4 days, and all of the animals survived, although each had received injections of 10 to 100 minimum lethal doses of virulent *Cl. welchii* (Fig. 6). In addition, the behavior and appearance of these guinea pigs were normal except for slight limping. The untreated animals receiving 1 or more minimum lethal doses died within 72 hours, demonstrating an extensive and fulminating gas gangrene (Fig. 7).

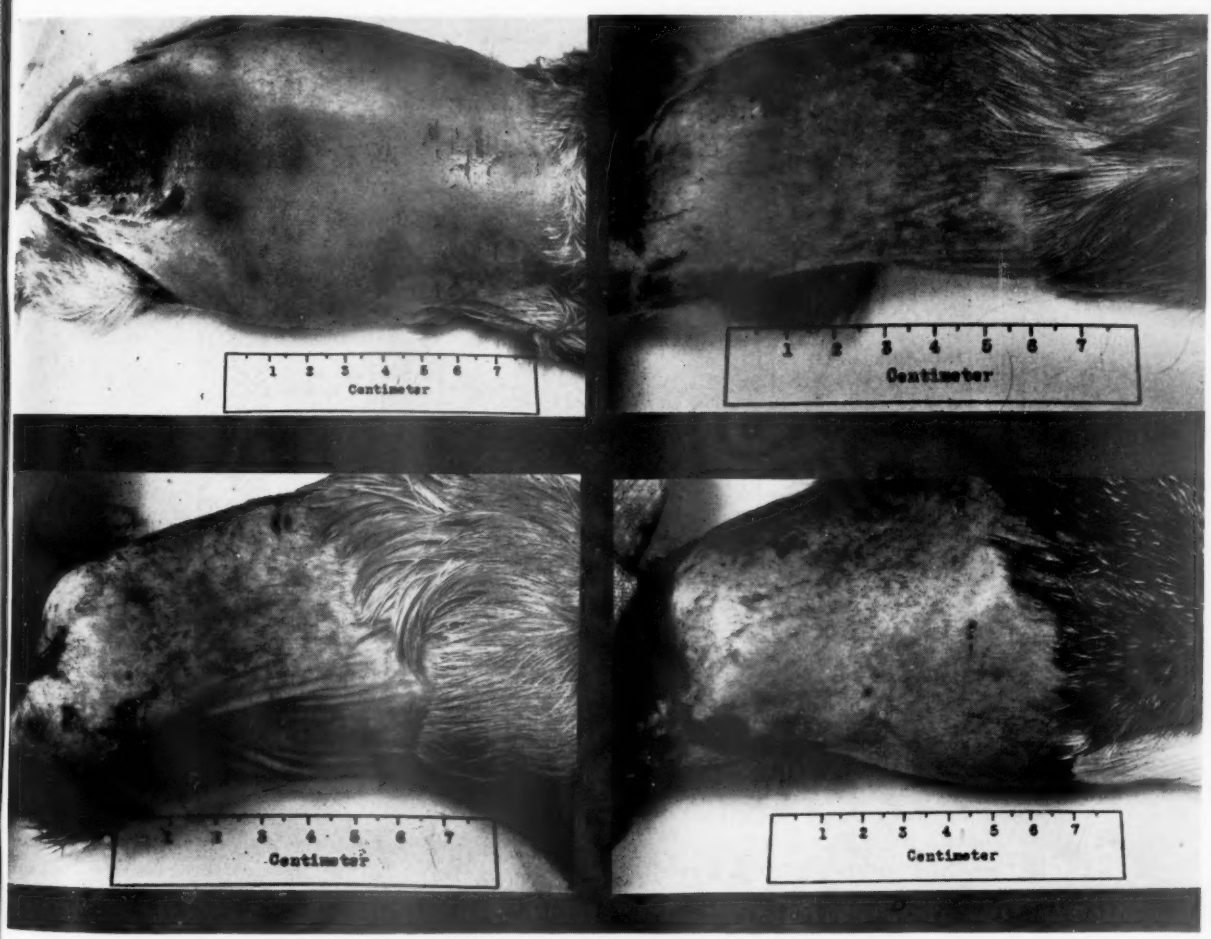


Fig. 5.—Photographs comparing the results on guinea pigs treated with Chloromycetin immediately after inoculation with 1 to 100 minimum lethal doses of *Cl. welchii* with those on untreated animals receiving a similar challenge. *A*, Untreated control with fulminating extensive gas gangrene producing death in 48 hours. *B*, Absence of gas gangrene in animal treated with 25 mg. of Chloromycetin per kilogram per day for 48 hours. Animal survived 10 minimum lethal doses of *Cl. welchii*. *C*, No evidence of infection in guinea pig challenged with 100 minimum lethal doses followed by treatment with 50 mg. of Chloromycetin per kilogram per day for 48 hours. Wound healed *per primam* and animal survived. *D*, No evidence of infection after challenge of 100 minimum lethal doses of *Cl. welchii* and treatment with 100 mg. of Chloromycetin per kilogram per day for 48 hours.

After cessation of aureomycin therapy, there was no visible evidence of delayed occurrence or exacerbation of the infection.

Aureomycin—Delayed Treatment.—When parenteral treatment with 20 mg. of aureomycin per kilogram per day was delayed for 4 hours, the control of the infection, which had already become established, was not as complete nor as definite as that previously observed when the therapy was started immediately. Nevertheless, a beneficial therapeutic effect on the course of the infection was noted in the animals of the delayed treatment group, although the effect was limited. In contrast to the controls, which exhibited extensive and fatal lesions, the guinea pigs treated with aureomycin showed a lower mortality rate and less extensive infections which developed more slowly. Only 50 per cent of the treated animals finally survived the infection.

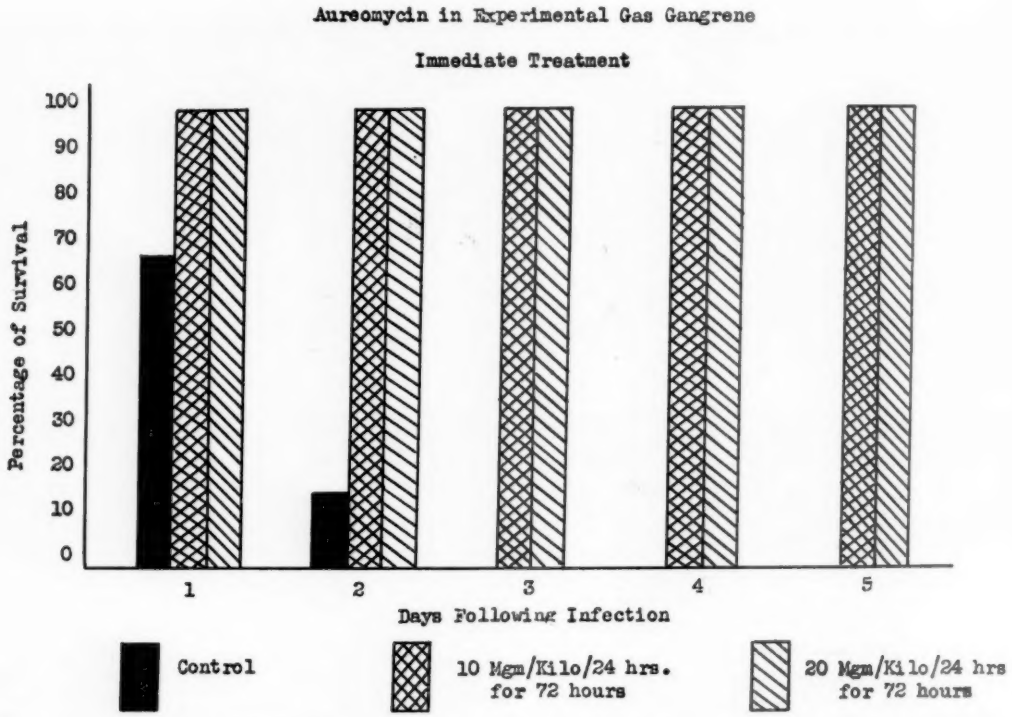


Fig. 6.—The marked chemotherapeutic effect of aureomycin is illustrated. Of the treated animals, 100 per cent survived experimental infection; 33⅓ per cent of controls died in 24 hours, 86⅔ per cent in 48 hours, and 100 per cent in 72 hours.

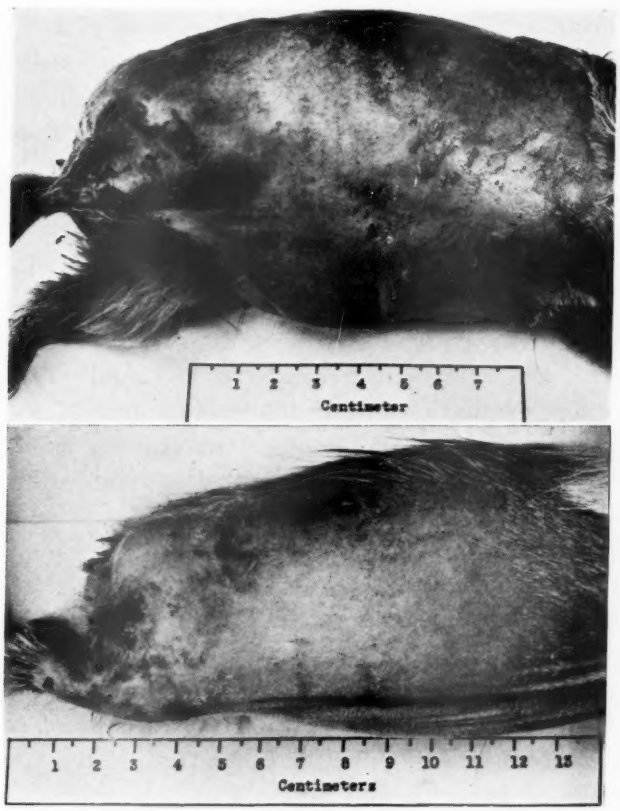
DISCUSSION

Both Chloromycetin and aureomycin have a remarkable chemotherapeutic effect for experimental gas gangrene when either is started in animals immediately after their injection with 1 to 100 minimum lethal doses of highly virulent cultures of *Cl. welchii*. The antibacterial effect of aureomycin for *Cl. welchii* in vitro is somewhat greater than that of Chloromycetin, but both appear to be at least as effective in vivo as penicillin.

Unfortunately, the therapeutic effectiveness of Chloromycetin in experimental gas gangrene has been somewhat obscured by variable degrees of toxicity

produced by the several glycols which are required as vehicles for the antibiotic agent's parenteral injection.* The toxicity of the various glycols varies and appears to be due to their action on the liver cells and renal tubules. Propylene glycol is the least toxic. The absence of any other suitable vehicle apparently limits the therapeutic possibilities of Chloromycetin for parenteral therapy at the present time.

A.



B.

Fig. 7.—Photographs illustrating the protective effect of aureomycin in experimental gas gangrene. *A*, Control or untreated animal with fulminating gas gangrene fatal in 48 hours. *B*, No evidence of infection developed in animal challenged with 100 minimum lethal doses of *Cl. welchii* and treated immediately with 20 mg. of aureomycin per kilogram for 72 hours.

On the other hand, aureomycin in leucine solution produced no evidence of toxicity and its chemotherapeutic effectiveness for experimental gas gangrene was more clearly shown. The difference in the appearance of the guinea pigs treated parenterally with Chloromycetin and aureomycin were very striking. The former group appeared listless, had little or no appetite, did not resist handling, and had poor muscular tone. The latter group showed none of these manifestations and did not deviate from the normal.

As in the case of penicillin and bacitracin, the earlier the beginning of aureomycin and Chloromycetin therapy, the greater and more obvious were

*Since the completion of this experiment, a nontoxic preparation of Chloromycetin suitable for parenteral use has been developed by the Parke, Davis & Company, Detroit, Mich.

the results obtained. Once the infection became well established, the effectiveness of chemotherapy was markedly diminished.

It was noted that the discontinuation of either Chloromycetin or aureomycin after 72 hours of therapy was not followed by the development of gas gangrene as previously occurred in similar experiments utilizing penicillin or bacitracin as the chemotherapeutic agents. This implies either a bactericidal effect of Chloromycetin and aureomycin, or sufficient suppression of the infecting agents that the normal defense mechanisms of the animals were able to effect the removal or disintegration of the bacteria.

No additional therapy, surgical or otherwise, was used in these experiments. This does not suggest, however, that either agent should be used in the absence of thorough débridement for the prevention of *Cl. welchii* infection, or in established clinical gas gangrene without early and thorough surgical decompression. In our experiments, the limitation of effectiveness of treatment of *Cl. welchii* infections established for 4 to 8 hours was at least partially due to the use of Chloromycetin or aureomycin alone and without surgery.

On the basis of these experiments, it would appear that parenterally administered aureomycin in average dosage is at least as effective as penicillin in massive dosage. Chloromycetin appears to be equally effective in higher doses but its complete evaluation awaits the development of a nontoxic vehicle. Oral administration of Chloromycetin was tried in one experiment, but the accuracy of the dosage and blood level concentrations were difficult to maintain.

SUMMARY

1. Chloromycetin and aureomycin both possess marked antibacterial activity in vitro for highly virulent strains of *Cl. welchii* isolated from war wounds complicated by gas gangrene.

2. The antibacterial effect of aureomycin is approximately 25 to 500 times greater in vitro than that of Chloromycetin for the strains of *Cl. welchii* tested.

3. Both agents are markedly effective in preventing the development of gas gangrene in wounds of experimental anima'ls.

4. The parenteral administration of Chloromycetin in 100 per cent propylene or polyethylene glycol for 72 hours was followed by the development of toxic changes in the liver and kidneys and death of approximately 25 per cent of animals. This toxic effect was due to the glycol and not to Chloromycetin. Animals treated with Chloromycetin in 20 to 50 per cent propylene glycol did not show toxic manifestations or mortality.

5. The parenteral injection of aureomycin in leucine solution for 72 hours was not complicated by any signs of toxicity or incidence of death in the treated animals.

6. Discontinuation of either agent after 72 hours in the animals treated immediately after inoculation of bacteria was not followed by development of gas gangrene.

7. The effectiveness of both agents was diminished and limited in established *Cl. welchii* infections.

8. Parenterally administered Chloromycetin and aureomycin in average dosage appear to be at least as effective as penicillin in massive doses for the prevention or treatment of severe experimental *Cl. welchii* infections similar to those occurring in man. More complete evaluation of Chloromycetin, however, awaits the development of a suitable and nontoxic vehicle for parenteral use.

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AN EVALUATION OF AUREOMYCIN AND CHLOROMYCETIN IN EXPERIMENTAL CLOSTRIDIUM WELCHII INFECTION

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WILLIAM P. WHARTON, B.S., AND RICHARD N. TAYLOR,
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THE laboratory experiments reported in this paper were conducted to appraise the prophylactic value of the antibiotics aureomycin and Chloromycetin in experimental *Clostridium welchii* infection in guinea pigs.

Aureomycin is produced by *Streptomyces aureofaciens* and Chloromycetin by *Streptomyces venezuelae*. Both are relatively nontoxic for man and have been used with effectiveness in a wide variety of infections caused by microorganisms.

In a series of experiments reported in detail elsewhere,[1] guinea pigs were protected by the prophylactic use of bacitracin against the development of infection with *Cl. welchii*, the organism most commonly associated with clinical gas gangrene in human beings. When two newer antibiotics became available it was decided to study their effect in similar experimental lesions. In vitro observations were made and it was found that both aureomycin and Chloromycetin in high dilutions were effective in preventing the growth of *Cl. welchii*. Encouraged by these results, the following animal experiments were conducted.

METHODS

Wounds were produced in anesthetized guinea pigs and contaminated with *Cl. welchii*. The study was conducted so that in each experiment one group of animals received a wound and a contaminating inoculum but was given no antibiotic and served as control, while another group of animals comparable in number and in weight received a wound, an identical contaminating inoculum, and an antibiotic. In principle the method used to produce the experimental lesion is that described in 1940 by Legroux.[2] The object of this investigation was to produce in guinea pigs lesions simulating war wounds contaminated with clostridia and to treat them with chemotherapeutic agents.

The Operation and Contamination.—The weights of the guinea pigs ranged from 200 to 796 Gm., but in most experiments animals weighing between 350 and 550 Gm., were used. The hair was removed from both hindquarters by clipping. The animals were anesthetized with sodium pentobarbital administered subcutaneously. The skin of one hindquarter and leg was scrubbed with a brush using soap and water, after which this area was sprayed with an antiseptic solution.* The operation was performed under aseptic technique. A skin incision 1 cm. in length was made over the gluteus maximus muscle of the animal.

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*Formula: $HgCl_2$ 0.7 Gm., tricresol 5 c.c., acetone 100 c.c., alcohol (95 per cent) 525 c.c., water 375 c.c.

After this muscle was exposed a portion of it was traumatized by crushing with a Kocher clamp. An effort was made to achieve uniformity in the size of the wound and the degree of trauma. The skin incision was then closed with cotton sutures and sealed with collodion. The latter steps were performed to reduce the probability of secondary contamination of the operative wound, to prevent loss of the bacterial inoculum, and to insure a relatively anaerobic environment in which the organisms could multiply. Finally the wound was contaminated by injection of bacteria through the adjacent normal skin into the traumatized

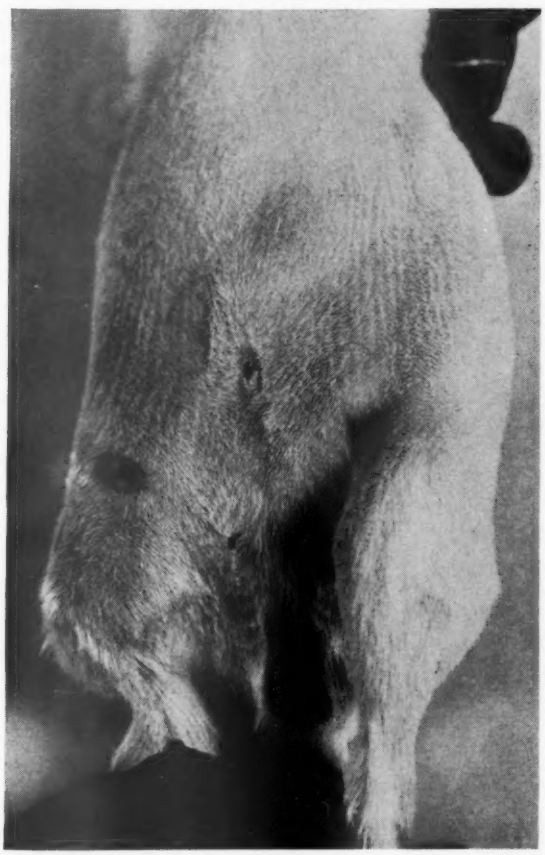

Fig. 1.—Photograph (anterior view) of a control animal taken one hour after death, which occurred 17 hours following wounding and contaminating with 0.1 c.c. of a culture of *Cl. welchii*. Note the extensive edema and discoloration of the right thigh, groin, and lower portion of the abdomen.

muscle, using a needle and syringe. Actively growing vegetative forms of *Cl. welchii** cultured from 4 to 5 hours in cooked beef heart medium in the amount of 0.1 c.c. were used to contaminate the wound. Before each experiment a gram-stained smear of the culture was made for the purpose of determining the purity of the culture. At the same time a serial dilution of a portion of the culture was made to determine the highest dilution in which the organism could be grown. This value for the separate experiments was as follows: 10^{-8} in one experiment; 10^{-9} in 5; 10^{-10} in 4; 10^{-11} in 1; and 10^{-12} in 15.

*The organism used was obtained from Dr. Frank L. Meleney of New York, who had originally received it from Dr. Ivan C. Hall. It is identified as Strain 1929.

The Prophylactic Use of Aureomycin.—In one series of controlled experiments aureomycin hydrochloride* was used as the antibiotic agent. This was dissolved in distilled water and was injected intramuscularly in the leg opposite the one that had been traumatized and contaminated. There was no evidence of any untoward reaction at the site of injection. In one group of experiments the drug was administered within 10 minutes after the operation and only a single

Fig. 2.—Photograph (anterior view) of an animal that was wounded and then contaminated with 0.1 c.c. of a culture of *Cl. welchii*. Within 10 minutes this animal received in the opposite thigh muscle aureomycin hydrochloride in the amount of 20 mg. per kilogram. This photograph was taken 23 hours following the operation and shows no evidence of infection. The animal survived the 13 day period of observation.

injection was given. The dosage was based upon the weight of the animal and is expressed in milligrams per kilogram of body weight. It ranged from 10 to 100 mg. In another group of experiments done with a relatively small number of animals a single injection of aureomycin hydrochloride* in the amount of 30 mg. per kilogram was administered at varying intervals following wound contamination, ranging from 5 or 10 minutes to 6 hours.

The Prophylactic Use of Chloromycetin.—In another series of controlled experiments Chloromycetin was used as the prophylactic agent. With the ex-

*The aureomycin used in these experiments was supplied by Lederle Laboratories, Division of American Cyanamid Co., New York, N. Y.

ception of one experiment (No. 74), these experiments were performed at a different time and entirely separately from those with aureomycin previously described. In this single experiment there were 10 control animals and 10 animals in each of the antibiotic groups. Crystalline Chloromycetin* dissolved in 50 per cent propylene glycol and alcohol was administered intramuscularly in the leg opposite the one that had been traumatized and contaminated. There was no evidence of any untoward reaction at the site of injection. With the

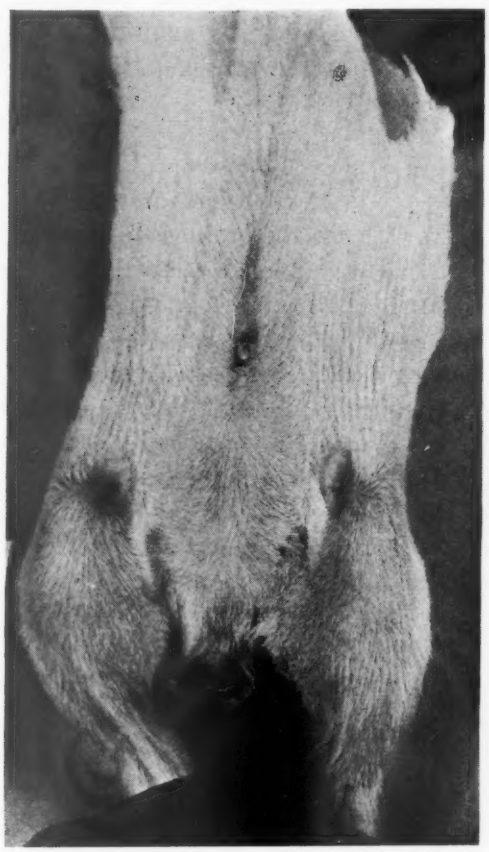

Fig. 3.—Photograph (anterior view) of an animal that was wounded and then contaminated with 0.1 c.c. of a culture of *Cl. welchii*. Within 10 minutes this animal received in the opposite thigh muscle Chloromycetin in the amount of 100 mg. per kilogram. This photograph was taken 18 hours following the operation and shows no evidence of infection. The animal survived the 13 day period of observation.

exception of one experiment the drug was given within 10 minutes following operation and was administered in a single dose. The amount was based upon the weight of the animal and is expressed in milligrams per kilogram of body weight. It ranged from 50 to 600 mg. In one experiment an initial dose of 200 mg. per kilogram was given within 10 minutes after wound contamination and was followed in 2 hours by 100 mg. and in 4 hours by another 100 mg.

Postoperative Observations.—Following operation each animal was kept in a separate, previously sterilized cage and offered a diet consisting of com-

*The Chloromycetin (chloramphenicol) used in these experiments was supplied by Parke, Davis & Co., Detroit, Mich.

mercially prepared food pellets, oats, and water. The animals were observed at frequent intervals with particular reference to their general state of health and the appearance of the local lesion. Every animal that died was subjected to a post-mortem examination and cultures were obtained from the tissue exudate in many of those that showed gross evidence of infection. All surviving animals were kept under observation for 13 days, then sacrificed and autopsied.

During the postoperative period the wound of a number of animals in the control, aureomycin, and Chloromycetin groups became infested with fly larvae. In most instances this wound complication made impossible the judging of results and therefore these animals are excluded from consideration in the statistical analysis of the series.

RESULTS

Clostridial Infection.—When infection occurred following wound contamination the clinical course of the guinea pigs and the gross pathologic lesions were characteristic. The animal developed swelling in the region of the wound which promptly spread so that the ipsilateral thigh was soon included. Usually before the animal died the process involved the groin and the abdominal wall and in some instances the thoracic and even the cervical regions. The swelling became noticeable in the region of the wound and in the wounded leg in approximately twelve hours and often reached the abdominal or thoracic walls within 18 to 24 hours. Most of the animals that survived infection for as long as 72 hours developed skin necrosis in the area immediately surrounding the site of operation. In some this necrosis was even more widespread, involving areas on the leg, groin, or abdominal wall. The infected animals looked ill. They were listless, inactive, and ate poorly. These signs progressed with the passage of time. At post-mortem examination, made in all fatal cases, in the area immediately surrounding the wound, the muscle was invariably pale, avascular, and necrotic, and often liquefied. Beyond this zone there were hemorrhagic congestion and edema of the muscle. In the adjacent subcutaneous tissue spaces there was an exudate more often serosanguineous, but occasionally slightly gelatinous. This was often extensive and seemed to accumulate in pockets in association with gas. Cultures taken from this exudate consistently yielded *Cl. welchii.*

Some animals survived the 13 day period of observation despite the fact that the process ultimately reached an advanced stage. These animals showed the same type of swelling as did those terminating fatally, with subsequent spontaneous wound disruption with the discharge of foul-smelling purulent material and finally ulceration and crust formation. When sacrificed and autopsied, there were varying degrees of muscle injury ranging from complete dissolution to slight superficial necrosis. In the tables recording the results these animals are classified as: "Survived with evidence of clostridial infection."

In the majority of the animals that did not develop active infection there was primary healing of the wound. In a few instances the operative wound became superficially ulcerated, but in no way showed any of the characteristics of clostridial infection.

TABLE I. AUREOMYCIN IN EXPERIMENTAL CL. WELCHII INFECTION*

CONTROLS	AUREOMYCIN				
Dose in milligrams per kilogram	none	10	20	30	50	100
Total number of animals	108	26	31	25	34	27
Survived without evidence of clostridial infection	0	9 (35%)	14 (45%)	17 (68%)	17 (50%)	12 (44%)
Died of causes other than clostridial infection	0	4 (15%)	8 (26%)	8 (32%)	17 (50%)	15 (56%)
Survived but showed clostridial infection	0	8 (31%)	3 (10%)	0	0	0
Died of clostridial infection	108 (100%)	5 (19%)	6 (19%)	0	0	0

*Results of experiments in which aureomycin was administered within 10 minutes after wound contamination. The contaminating inoculum consisted of 0.1 c.c. of a 4 to 5 hour culture of *Cl. welchii*. The controls received a contaminating inoculum but no aureomycin.

Aureomycin.—The results in the aureomycin experiments in which the drug was administered within 10 minutes after wound contamination are recorded in Table I. This table shows that aureomycin in the amount of 30 mg. or more per kilogram protects guinea pigs from death due to experimental *Cl. welchii* infection. The results in those experiments in which the drug in the amount of 30 mg. per kilogram was administered at varying intervals ranging from 5 or 10 minutes to 6 hours after wound contamination are recorded in Table II. This table shows that the protection against *Cl. welchii* afforded by aureomycin is effective if the drug is given within the first 2 hours after contamination of the experimental wound but is lost if administration of the drug is delayed beyond 2 hours.

TABLE II. AUREOMYCIN IN EXPERIMENTAL CL. WELCHII INFECTION
Interval Between Wound Contamination and Administration of Aureomycin Hydrochloride (30 mg. per Kilogram)*

	CONTROLS	5-10 MIN.	1 HOUR	2 HOURS	3 HOURS	4 HOURS	5 HOURS	6 HOURS
Total number of animals	9	8	10	8	9	8	10	9
Survived without evidence of clostridial infection	0	6	6	3	2	0	0	0
Died of causes other than clostridial infection	0	2	4	5	0	2	0	2
Survived but showed clostridial infection	0	0	0	0	1	0	0	0
Died of clostridial infection	9	0	0	0	6	6	10	7

*The results of experiments in which aureomycin hydrochloride in the amount of 30 mg. per kilogram was administered at varying intervals ranging from 5 or 10 minutes to 6 hours after wound contamination. The contaminating inoculum consisted of 0.1 c.c. of a 4 to 5 hour culture of *Cl. welchii*. The controls received a contaminating inoculum but no aureomycin.

TABLE III. RESULTS OF EXPERIMENTS IN WHICH CHLOROMYCETIN WAS ADMINISTERED WITHIN TEN MINUTES AFTER WOUND CONTAMINATION*

EXPERIMENT NUMBER	60B	58	59	61B	62B	60A	61A	62A	65	66	67	68	69	72	73	74
CONTROLS																
Total number of animals	8	9	7	5	7	See 60B	See 61B	See 62B	8	12	9	12	9	6	12	10
Survived without evidence of clostridial infection	3	1	0	0	0				1	0	2	0	0	0	0	0
Died of causes other than clostridial infection	0	0	0	0	0				0	0	0	0	0	0	0	0
Survived but showed evidence of clostridial infection	0	0	1	0	1				0	0	0	1	0	0	0	0
Died of clostridial infection	5	8	6	5	6				7	12	7	11	9	6	12	10
CHLOROMYCETIN (dose in milligrams per kilogram)	50	100†	100†	100	100	200	200	200	300	300	300	400	400	400	600	200‡ 100 100
Total number of animals	7	9	9	4	8	8	3	8	8	5	10	11	8	6	11	10
Survived without evidence of clostridial infection	5	9	6	2	6	7	2	7	5	1	6	11	7	1	0	0
Died of causes other than clostridial infection	0	0	3	1	1	0	0	1	1	0	0	0	1	0	0	3
Survived but showed evidence of clostridial infection	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Died of clostridial infection	2	0	0	1	0	1	1	0	2	4	4	0	0	5	11	7

*The contaminating inoculum consisted of 0.1 c.c. of a 4 to 5 hour culture of *Cl. welchii*. The controls received a contaminating inoculum but no Chloromycetin.

†In Experiments 58 and 59, 100 mg. of Chloromycetin were given to each animal irrespective of the weight of the animal, which ranged from 474 to 564 Gm.

‡In Experiment 74, 200 mg. per kilogram of Chloromycetin were given within 10 minutes after operation, and 100 mg. per kilogram were given 2 and 4 hours later.

It is to be noted in the aureomycin experiments that some of the animals receiving this drug died of causes other than clostridial infection. These animals lived longer than the controls, 7⅔ days as compared with 19 hours, and when autopsy was performed no evidence of clostridial infection was present. Most of them showed pulmonary consolidation but aside from this abnormality no other gross lesion could be found. A few had diarrhea during life. Moreover, it was noted in several experiments that guinea pigs receiving large doses of aureomycin showed progressive weight loss. On the basis of these observations the cause of death is not adequately explained, but in view of the parallel between the mortality rate and the amount of drug administered, toxic manifestations of aureomycin peculiar to the guinea pig must be kept in mind as a possibility.

Chloromycetin.—The results in the experiments with Chloromycetin are recorded in Tables III and IV. In Table III the result of each experiment is recorded, while in Table IV the results of all experiments with the exception of 73 and 74 are summarized. The reasons for excluding these two experiments from the summarizing table are discussed later.

TABLE IV. CHLOROMYCETIN IN EXPERIMENTAL CL. WELCHII INFECTION*

	CONTROLS	CHLOROMYCETIN
Dose in milligrams per kilogram	none	50 TO 400
Total number of animals	92	104
Survived without evidence of clostridial infection	7 (8%)	75 (72%)
Died of causes other than clostridial infection	0	8
Survived but showed clostridial infection	3	1
Died of clostridial infection	82 (89%)	20 (19%)

*A summary of the results in experiments recorded in Table III, with the exception of Experiments 73 and 74. Chloromycetin was administered within 10 minutes after wound contamination. The contaminating inoculum consisted of 0.1 c.c. of a 4 to 5 hour culture of *Cl. welchii*. The controls received a contaminating inoculum but no Chloromycetin.

Table III shows that 72 per cent of the animals that received a single injection of Chloromycetin in amounts ranging from 50 to 400 mg. per kilogram were protected from death due to clostridial infection. The difference in survival rates between the control animals and those receiving Chloromycetin shortly after wound contamination is of statistical significance and indicates that this drug is of value in protecting guinea pigs against experimentally produced clostridial infection.

Only 89 per cent of the control animals in the study with Chloromycetin died of clostridial infection. This is a matter unexplained and the cause of some concern since in a previously reported[1] study 96 per cent of 180 control animals died of clostridial infection and in the present study with aureomycin a mortality rate of 100 per cent among the control animals has been attained.

DISCUSSION

In the study with Chloromycetin 2 experiments (73 and 74) are recorded in Table III but excluded from the summarizing Table IV. It is to be noted that every animal, both treated and control, died. Since the number of animals in these 2 experiments is too small to be of statistical significance and since they are at variance with the results in the earlier experiments they are not included in the summary and are not made use of in drawing conclusions in the present report. Further observations are indicated in an effort to clarify this paradoxical result.

It is to be emphasized that no comparison is to be made between the prophylactic effectiveness of aureomycin and Chloromycetin on the basis of these observations. With the exception of the 1 experiment previously noted, these studies were not run as parallel experiments but at separate times, and, although the same organism was used in both studies, possible difference in behavior on different days invalidates any comparisons which one may be tempted to make. Moreover, it is highly probable that maximum prophylaxis with Chloromycetin has not been attained and that further alterations in dosage or method of administration or both will be required to achieve full effectiveness with this drug.

In consideration of possible application to clinical surgery, a paragraph from the report[1] of a parallel study with bacitracin may be quoted: "Although the clostridial infection produced by the method herein described simulates clinical gas gangrene in human beings, it is not identical with it. There are a number of differences. The contamination in these experiments was undoubtedly proportionately more massive than that usually occurring in traumatic wounds in human beings. Moreover, the organisms entered the wound in an actively multiplying state, whereas in the usual clinical wound the contaminating clostridia enter in the spore form. Thus, for comparable intervals following contamination, the experimental lesion is apt to be further advanced bacteriologically than is the clinical wound. Gas gangrene in the human being is usually polymicrobial whereas in these experiments only 1 organism was used. In the mixed flora of the clinical case there may be organisms which produce substances that inactivate an antibiotic otherwise effective against the clostridial flora of the wound."

SUMMARY AND CONCLUSIONS

Experiments were conducted in which wounds were produced in anesthetized guinea pigs and contaminated with *Cl. welchii.* Untreated control animals developed lesions simulating clinical gas gangrene in human beings. The antibiotics, aureomycin and Chloromycetin, administered intramuscularly, were used in separate series as prophylactic agents.

The results of the studies with aureomycin indicate that this drug administered intramuscularly in doses of 30 mg. or more per kilogram shortly after wound contamination protects guinea pigs from death due to clostridial infection. The high mortality rate from causes other than clostridial infection among animals receiving aureomycin is not adequately explained.

In the studies with Chloromycetin the difference in survival rates between the control animals and those receiving Chloromycetin shortly after wound contamination is of statistical significance and indicates that this drug is of value in protecting guinea pigs against death from experimentally produced clostridial infection.

Due to possible differences between infection in the laboratory animal and in the human being, the interpretation of these results must be applied with caution to the clinical problem. However, they do suggest that these 2 antibiotics may prove valuable adjuncts to other well-recognized methods in the treatment of clinical gas gangrene in the human being.

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MYOMATOUS TUMORS OF THE RECTUM (LEIOMYOMAS AND MYOSARCOMAS)

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LEIOMYOMAS and leiomyosarcomas occur anywhere in the gastrointestinal tract. Leiomyoma is found twice as often in the stomach as in the small bowel, colon, and rectum combined. Excluding esophageal tumors, the incidence of leiomyomatous tumors of the gastrointestinal tract in our series is approximately as follows: stomach, 65 per cent; small intestine (including Meckel's diverticulum), 25 per cent; colon, 3 per cent; rectum, 7 per cent.

The great majority of gastrointestinal myomatous neoplasms of the stomach are benign. Eighty per cent of those which occur in the small bowel are malignant. Approximately one-half of those found in the colon and rectum are malignant. Much has been written about smooth-muscle tumors of the upper part of the gastrointestinal tract and colon. No comparable study has been made of leiomyomas and leiomyosarcomas of the rectum. It was with this purpose in mind that the present study was undertaken. It is felt that this work is of special interest because smooth-muscle tumors of the rectum present an entirely different problem from that of similar lesions found elsewhere in the body.

REVIEW OF LITERATURE

Ewing[3] wrote that benign leiomyomas in the intestinal tract are not uncommon, and that they may be single or multiple. He did not mention myomatous tumors of the rectum.

Verified myoma of the rectum apparently was first reported in 1881 by Vander Espt.[11] Four cases of leiomyoma of the rectum were reported by Hunt,[8] in 1921, who stated that 20 cases of myoma or myofibroma had been reported in the literature up to 1921. Constipation, rectal pain, and hemorrhage were the three main symptoms mentioned.

In 1932, Rankin and Larson[10] reported 4 cases of myosarcoma of the rectum, and reviewed the literature on the subject. The majority of malignant myomas were said to have affected males, in contradistinction to the situation observed with leiomyomas of the rectum. The authors emphasized that although these tumors were of slow evolution and late to metastasize, results following local extirpation were disappointing, and the patients often succumbed to metastasis. They felt that therapy with roentgen rays was of very little value.

In 1933, Hartmann, Bertrand-Fontaine, and Guérin[7] reported a case of leiomyoma of the rectum and reviewed the literature on the subject. They found

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that 37 cases had been reported up to 1933, and noted that 20 of the tumors had occurred in females and 15 in males. The situation of the 6 tumors in the other 2 patients was not given.

In 1934, Geschickter[4] made a comprehensive survey of muscle tumors of the gastrointestinal tract found in the surgical laboratories of the Johns Hopkins Hospital. He found that of 25 benign leiomyomas of the gastrointestinal tract, 1 was situated in the rectum. Of 3 gastrointestinal leiomyosarcomas, 1 was situated in the stomach, 1 in the ileum, and 1 in the rectum.

Golden and Stout,[5] in 1941, reported that in 5 of 30 cases of smooth-muscle tumors of the gastrointestinal tract the lesion was primary in the rectum.

Of 47 cases of submucosal nodules of the rectum reported in 1944 by Jackman and one of us (Buie),[9] only 1 (2.1 per cent) was a case of leiomyoma.

Goldman and Marbury,[6] in 1946, wrote that 150 cases of sarcoma of the rectum had been reported up to 1946, and that in 8 of these cases the lesions were leiomyosarcomas.

MATERIALS AND METHODS

This review is based on a study of 10 cases of leiomyoma and 10 cases of leiomyosarcoma of the rectum recorded in the files of the Mayo Clinic from 1911 to 1946. All the lesions were removed surgically or specimens of them had been taken for biopsy, and the specimens were preserved in 10 per cent solution of formalin. The gross features were observed and blocks were cut from selected areas. Slides were prepared by both the freezing and the paraffin methods, and were then stained with hematoxylin and eosin.

Careful review of the clinical records was made in each case and particular emphasis was placed on symptoms, diagnostic signs, type of treatment employed, and results.

PATHOLOGIC FINDINGS

While discussing the general question of the pathologic aspects of leiomyomas, both gross and microscopic, we wish to quote from Bell,[1] who summarizes this problem clearly and concisely:

> Leiomyoma is a tumor composed of smooth muscle. It is a very common tumor, more often multiple than single, developing usually from tissues containing smooth muscle. These growths vary enormously in size, are usually firm or even hard and show a fibrous cut surface. Less frequently they are of looser texture and soft and the rare vascular forms may resemble angiomas. Regressive changes may bring about softening or disintegration of part of the tumor or calcification. There is usually a slow, progressive enlargement over a period of years sometimes with complete cessation of growth or there may be periods of rapid increase in size. Sometimes the rate of growth becomes so rapid that the tissue assumes an embryonic type and is not recognizable as muscle (leiomyosarcoma) and in rare instances such tumors may form metastasis. The structure of slowly growing leiomyomas approaches that of adult smooth muscle. It may be distinguished from spindle cell sarcoma only by the structure of other parts of the tumor. Hyaline degeneration is a very common retrogressive change.

There are three places from which a smooth-muscle tumor may arise in the rectal wall; namely, the muscularis mucosae, the circular and longitudinal muscle layers, and the walls of the blood vessels.

When distinguishing a leiomyoma from a leiomyosarcoma we have followed the microscopic criteria of malignancy in smooth-muscle tumors as outlined by Evans[2] in 1920. We have employed Broders' classification for determination of the grade of malignancy of our 10 malignant tumors.

Leiomyoma of the Rectum: 10 Cases.—

Gross: Five of the leiomyomas arose from the anterior rectal wall, 3 from the lateral wall, and 2 from the posterior wall. Of the 5 arising from the anterior wall, 2 were outgrowths of the rectovaginal septum. Of the 3 tumors situated on the lateral wall, 2 were on the left side and 1 was on the right. Of the 2 situated on the posterior wall, 1 extended back into and occupied part of the retrocecal space, and the other projected into the rectal lumen. All of these 10 benign leiomyomas were situated from 2 to 4 cm. orad to the dentate line.

All the benign tumors were small. They varied from 5 mm. to 5 cm. in diameter. The largest extended into the retrorectal space. The average diameter was about 1 cm.

The tumors were spherical and encapsulated, and varied from white to reddish brown. Seven were submucosal nodules. One was complicated by a subacute abscess. This is the reverse of the usual sequence. A growth was not suspected until after the specimen had been sent to the laboratory for histologic diagnosis. One tumor was felt as a nodule in the pelvirectal space.

In none of the 10 cases was the overlying mucosa ulcerated and in only 1 was the mucosa attached to the tumor. In the other 9 cases the overlying mucosa was freely movable.

Eight of the tumors were firm in consistency; 2 were soft.

There was no fixation of any of these tumors to the surrounding structures.

Microscopic features: Microscopically, all 10 of these tumors (Fig. 1*a*) showed the typical structure of encapsulated leiomyomas in that they approached the structure of adult smooth muscle. They had the typical rod-shaped nuclei of benign leiomyomas. There was no variation in the size of the tumor cells. The nuclei did not vary in degree of staining. The presence of unusual tumor cells, such as giant cells, was not noted and no definite mitotic figures were seen.

Leiomyosarcomas of the Rectum: 10 Cases.—

Gross: Of the 10 malignant tumors, 5 arose from the posterior wall, 4 arose from the lateral walls, and only 1 arose from the anterior wall. All 10 of the tumors were situated between the dentate line and a level 6 inches proximal to it.

The malignant specimens varied greatly in size. The smallest specimens were 2 cm. in diameter and the largest was 8 by 5 by 5 cm. One of the tumors was described, on the clinical chart, as being the size of a hen's egg; another was described as being the size of a grapefruit.

A brief description of each of the 10 tumors follows. In this description are combined the findings made at digital examination, the proctologic observations, and the pathologic reports.

CASE 1.—On the lateral rectal wall just within the sphincter was a tumor mass with an ulcerated crater in the center, 1.5 inches deep. The tumor was fairly well circumscribed, irregular in shape, but not encapsulated (Figs. 1*b* and 2).

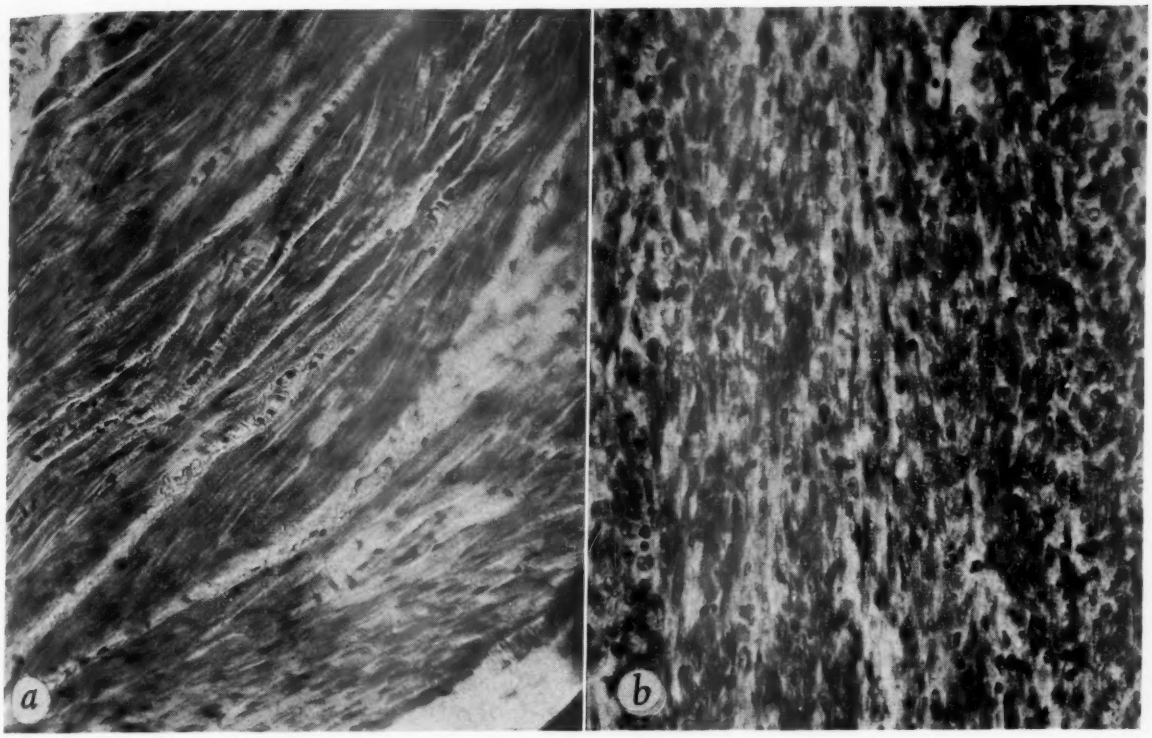

Fig. 1.—*a*, Benign leiomyoma of the rectum: compare with sections in Figs. 1*b* and 3; note excellent polarity of the cells and the large amount of stainable cytoplasm; secondary fibrosis is present in this example (hematoxylin and eosin ×100); *b*, portion of the grade 2 leiomyosarcoma illustrated in Fig. 2. Although polarity is well preserved, the lesion is fairly cellular and mitotic figures are easy to find. The grade of malignancy is 2 on the basis of 1 to 4 (Broders' method) (hematoxylin and eosin ×235).

Fig. 2.—Ulcerating leiomyosarcoma of the rectum associated with a small benign leiomyoma about 2 cm. above the large lesion on the illustration. In spite of radical removal of this tumor, the patient died from the effects of generalized abdominal metastasis 5 years after operation.

CASE 2.—On the posterior wall of the rectum an egg-sized tumor was felt. It did not extend into the lumen of the bowel but developed posteriorly. It was firm in consistency, encapsulated, and brownish. The weight of the tumor was 155 Gm. The mucosa was not ulcerated.

CASE 3.—Extending posteriorly from the rectum was a tumor the size of a grapefruit. It was soft in consistency, brownish, and the mucosa was not ulcerated. The tumor involved the surrounding structures.

CASE 4.—On the left wall of the rectum, beginning at the dentate margin and extending orad for 6 cm., was a smooth, firm, movable, submucosal mass that was grayish, lobulated, and 4 by 5 by 3 cm. The mucosa was not ulcerated (Fig. 3).

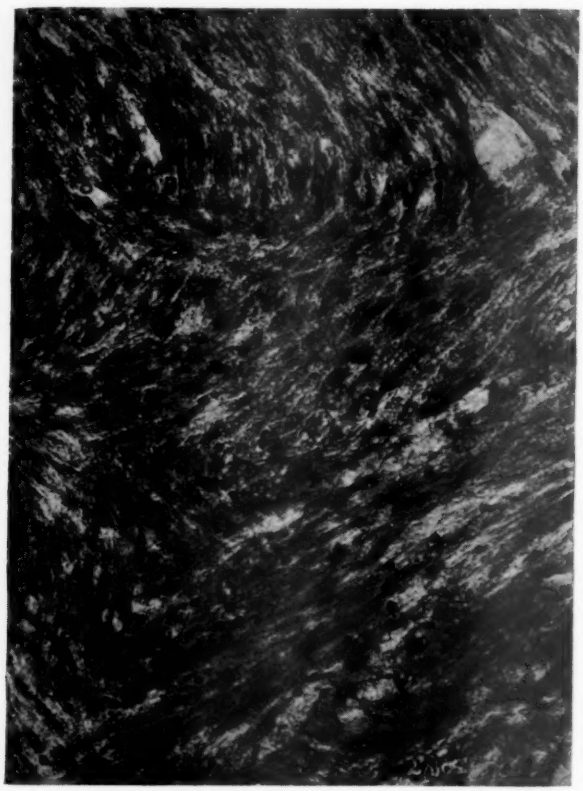

Fig. 3.—Well-differentiated grade 1 leiomyosarcoma of the rectum. Distinction from benign leiomyoma is made on the basis of moderately increased cellularity and the presence of an occasional mitotic figure. The patient who had this tumor died 7 years after wide local excision of what appeared to be a well-encapsulated lesion (hematoxylin and eosin ×235).

CASE 5.—Just orad to the dentate line was a firm, smooth, tumor mass 6 cm. in diameter. On cut section, the tumor was found to be of firm consistency, brownish, and encapsulated. The mucous membrane was not ulcerated.

CASE 6.—There was an ulcerating mass on the posterior rectal wall 6 cm. orad to the dentate line. Only a specimen for biopsy was removed.

CASE 7.—Two centimeters orad to the dentate margin was a tumor mass 5 by 5 by 4 cm. It was soft and brownish gray. There was an area of ulceration in the mucosa 2 cm. in diameter. Just lateral to the large lesion was a submucous benign leiomyoma 1 cm. in diameter.

CASE 8.—On the posterior wall of the rectum 6 cm. orad to the anus was a large, smooth, fixed tumor 8 by 4 by 4 cm. In the mucosa there was an area of ulceration in the center of the lesion 2 cm. in diameter. The tumor protruded into the rectal lumen.

CASE 9.—To the right and posterior to the rectum was a lobulated, encapsulated, and very firm tumor mass 5 by 4 inches. It was brownish, did not intrude on the lumen of the bowel, and "shelled out" easily. The mucosa was not ulcerated.

CASE 10.—Beginning just orad to the dentate line on the right rectal wall was a tumor the size of a small orange. It was firm, movable, but infiltrated, and the mucosa showed an area of ulceration 2 cm. in diameter. The tumor was encapsulated and brownish, and it encroached on the lumen of the bowel.

In summary, it may be said of this series of 10 leiomyosarcomas that 5 had produced ulceration of the mucosa and 5 had not. The ulceration was characterized by a rather punched-out or umbilicated appearance. The ulcers were small and their bases were quite deep.

The tumors varied from soft to very firm. Five of these tumors were fixed to surrounding structures. The tumors varied from gray to brown. All of these tumors were of the sessile type. None was polypoid. No annular or napkin-ring type of lesion was encountered.

Microscopic features: The grades of malignancy varied widely. Specimens of a low grade approached adult smooth muscle in appearance, and some of them required very careful study for the demonstration of evidence of malignancy. The presence of mitoses was helpful in deciding the issue. Tumors of a high grade of malignancy exhibited all the criteria of leiomyomatous malignancy as outlined by Evans,[2] such as increase in the size of tumor cells, shorter and plumper forms with more oval nuclei, inequality in the size and shape of the cells, lack of differentiation, unequal and especially deep staining of the nuclei, presence of giant cells, many normal and pathologic mitoses, decrease of stromal fibers, and thinness and occasional absence of walls of blood vessels.

Five of these tumors were classified as grade 1 (Broders), 3 were classified as grade 2, and 2 were classified as grade 4.

In only 2 of these tumors could the exact point of origin be determined. These 2 arose from just beneath the mucosa in the region of the muscularis mucosae. In the other cases such complete involvement of the rectal wall was observed that we could not determine whether the tumors arose from the muscularis mucosae, the walls of the blood vessels, or the muscularis propria of the rectum.

Glandular metastasis of leiomyosarcomas is mentioned rather frequently, but in this series of 10 cases we were unable to demonstrate any involvement of lymph nodes.

CLINICAL PICTURE

Leiomyoma of the Rectum.—This benign tumor is very rare, being encountered once in every 2,000 or 3,000 rectal tumors. In our series of 10 leiomyomas of the rectum, the youngest patient was 28 years of age and the oldest was 61 years of age. The average age was 47 years. Seven of the patients were women and 3 were men.

In only 1 of the 10 cases was there any gross bleeding, and none of the patients complained of pain. No change of bowel habit was encountered in any of this series. No patient gave any history of symptoms of a general nature such as loss of weight, weakness, and anorexia. There were no significant symptoms in any instance, and all the tumors were detected incidentally during routine physical examinations.

Proctoscopic examination revealed the presence of a tumor mass in 6 cases, but did not reveal any lesion in 4 cases.

The diagnoses in 9 of this series of cases were established by the finding of a submucosal nodule on digital examination and removal of this nodule and histologic examination of it. One of the lesions was found in routine histologic examination of tissue excised at fistulectomy.

Operation in the entire series consisted only of local excision.

No history of recurrence was encountered among any of the patients, and the length of time ensuing after operation varied from 1 year to 39 years.

Leiomyosarcomas of the Rectum.—This tumor, as we have said, is rare, but it is well to remember that 50 per cent of rectal leiomyomatous tumors are malignant.

The incidence according to age in the series of 10 leiomyosarcomas varied from 34 to 76 years. The average age of a patient was 54.5 years. The incidence according to sex was exactly reversed from that of the benign leiomyomas, there being 7 men and 3 women.

In 4 of the cases there was gross bleeding; in 6 there was no blood. Five of the 10 patients experienced a change in bowel habit; 3 of these 5 suffered progressive constipation and 2 had alternate constipation and diarrhea. The remaining 5 patients had no change in bowel habit. Only 3 of the 10 patients exhibited any generalized symptoms, and these consisted of anorexia, loss of weight, and weakness. Seven of the patients complained of definite localized rectal pain; 1 complained only of a very indefinite type of pain. Two patients in the series had no pain.

All the lesions in this series were seen through the proctoscope; 5 had produced ulceration of the mucosa.

All 10 of the tumors could have been felt by digital examination, but the exact diagnosis was not made or even suspected in any of the 10 cases until tissue removed for microscopic examination had been reported on.

Two of the 10 patients immediately underwent abdominoperineal resection. One died postoperatively. Two patients were treated by local excision of the tumor followed by radium. Both died of metastasis. One patient underwent local excision of the tumor with no other therapy, and later was reported dead of metastasis. One patient underwent local excisions 3 times over a period of 6 years because of local recurrence, and died of another local recurrence. Another patient underwent local excision and the application of radium 4 times over a period of 8 years. Each operation was followed by a recurrence. We were unable to find out what happened to this patient; follow-up letters were not answered. One patient underwent local excision of the tumor 3 times, and

because the lesion recurred the third time, abdominoperineal resection was done. The history of this surgical management was spread over a period of 4 years. The patient was reported by her local physician to have died of metastasis 3 years after the abdominoperineal resection. Another patient received radium therapy. This patient returned 9 months later, and abdominoperineal resection was done because of a recurrence. She died 1 year later from metastasis to the liver and spinal column. One patient, 76 years of age and in very poor condition, had an extensive grade 4 lesion of the rectum. Because of her general condition, radium alone was used. She was reported dead of metastasis 2 years later.

Comment on Leiomyosarcomas of the Rectum.—Nine patients were dead at the time this study was completed. One had repeated recurrences after local excision. The status of this patient at the time of this writing could not be determined because follow-up letters were not answered. Abdominoperineal resection of the rectum, as the first mode of treatment, was used in only 2 cases. One patient was treated by multiple local excisions followed by abdominoperineal resection. The others were treated by local excision; radium also was used in 3 cases.

The life span of the patients with grade 1 and grade 2 leiomyosarcomas, from the time of the first operation or treatment, was 2 to 15 years. Of the 2 patients with grade 4 lesions, 1 lived 2 years and 1 lived 7 months. The average length of life from the time of the first operation in this entire group was 5.2 years.

SUMMARY AND CONCLUSIONS

Fifty per cent of smooth-muscle tumors of the rectum are benign and 50 per cent are malignant. Benign leiomyomas are asymptomatic and usually are detected during routine physical examination. Benign leiomyomas usually are small, and the majority of them are best described as "submucosal nodules." Benign lesions affect chiefly women; malignant lesions predominate among men. Local excision is sufficient for eradication of a benign leiomyoma.

Symptoms most commonly encountered in leiomyosarcoma were bleeding, change in bowel habit, rectal pain, and certain generalized symptoms such as a weakness, anorexia, and loss of weight. Leiomyosarcomas were rather large; 50 per cent had produced ulceration of the mucosa. Leiomyosarcomas of the rectum are highly dangerous lesions; 9 of this series of 10 patients are known to have died of their diseases and the tenth had a recurrence when last heard from. Local excision of leiomyosarcomas of the rectum is almost invariably followed by recurrence, no matter what the grade of malignancy. All leiomyosarcomas, from the lowest to the highest grade of malignancy, should be attacked by some radical type of rectal resection as soon as the diagnosis has been established. Distinction between a benign leiomyoma and a leiomyosarcoma often is very difficult, requiring very careful microscopic study. Radium therapy seems to have no effect on the eventual outcome in leiomyosarcomas of the rectum, which show a marked tendency toward local recurrence over a long period before they eventually metastasize. Any submucosal nodule of the rectum should be considered as being a possibly dangerous lesion and therefore should be excised.

In this series of 10 leiomyosarcomas of the rectum we were unable to demonstrate any metastasis to lymph nodes, although some of the patients died later from abdominal sarcomatosis.

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ADENOMAS OF THE COLON AND RECTUM

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THE problem of adenomas of the colon is an example of modern methods of medicine in reverse; while the treatment of these lesions now rests on a solid foundation of clinical knowledge and experience, little, if anything, is known about the cause. One pathologist likes to designate many of these epithelial growths of the colon as histologically malignant but clinically benign.[1] In this paper adenomas are defined as pedunculated or sessile glandular structures which exhibit proliferation of colonic epithelium without invasion of the intestinal wall.[2]

Adenomas have been studied in several ways: (1) periodic endoscopic observations of the lesion combined with repeated biopsies; (2) histologic studies of segments of colon surgically removed, usually for cancer, and at times for benign lesions, such as diverticulitis, submucous lipoma, and so forth, and (3) comprehensive investigations of the entire colon at necropsy.

Personally conducted endoscopic studies in 2 fairly large, separate groups of individuals have revealed some interesting data.[2] Routine sigmoidoscopic investigation of 386 consecutive patients with average ages of 50 years or more, who had intestinal symptoms, particularly bleeding from the rectum, revealed adenomas in 27 individuals. (This figure does not include mucosal excresences which are now regarded as tiny adenomas by many authors.) In 4 additional patients adenomas above the reach of the sigmoidoscope were detected by barium and air double-contrast roentgenography of the colon. Thus, an incidence of over 7 per cent of histologically verified lesions was elicited in symptomatic individuals. Significantly, the bodies of 5 of these pedunculated adenomas contained malignant foci. Malignancy developed after a lapse of approximately 3 years in sessile adenomas of 2 other patients who refused treatment.

A similar, consecutive number of individuals under the age of 45 without intestinal complaints were subjected to sigmoidoscopy, visualizing a distance of 25 cm. or more of the terminal bowel. This study revealed 7 adenomas (and 9 mucosal excrescences varying in size from 1 to 4 mm.), giving an incidence of adenoma of approximately 2 per cent, exclusive of mucosal excrescences. This 2 per cent held true for an additional 1,005 men thus examined.

It was felt that this series of patients might lend itself to a study of the possible transition of adenoma to carcinoma by periodic observation and biopsy of the adenomas of selected individuals. However, as this investigation progressed, it became clear that such a clinical experiment has little chance of success, primarily because of the difficulty of inducing patients to cooperate in a long-range project. This point is clearly illustrated by the behavior of 2 very intelligent individuals: 1 disappeared after only 1 re-examination, while the

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second developed cancerphobia, necessitating the immediate extirpation of the adenoma under observation.

The study of surgically removed specimens, although valuable, has, nevertheless, obvious limitations. On the other hand, studies of colons removed at necropsy have contributed much to our knowledge and understanding of adenomas of the colon. Comprehensive combined clinical and post-mortem investigations would be most desirable, but they are unfortunately lacking.

PATHOGENESIS AND MORPHOLOGY

Adenomas appear to originate as epithelial proliferation or hyperplasia from a normal, flat, or folded mucous membrane[3] with normal physical and physiochemical function, which may terminate as uncontrolled, disorderly growth exhibiting loss of normal physical appearance and physiochemical function.[4]

Neither lymphoid nodules nor antecedent inflammatory processes are prerequisites for the development of adenomas.[1, 3] The presence of lymphoid nodules appears to be purely coincidental, although, clinically, an occasional benign or malignant adenoma may appear to have resulted from a long-standing chronic inflammation of the colon such as ulcerative colitis. However, there is no clear-cut pathologic evidence substantiating this possibility. It is reasoned that such an inflammatory process would surely leave some evidence of inflammation, atrophy, or fibrosis which was found to be absent in the pathologic studies of Helwig.[3] Individual adenomas may be subjected to considerable trauma, as evidenced by the presence of hemorrhage and deposits of hemosiderin within the stroma of the polyps. These growths, especially the larger ones, may also contain inflammatory cells, such as neutrophilic and eosinophilic polymorphonuclear leucocytes, lymphocytes, monocytes, and so on.

Adenomas occur at practically all ages, the incidence being highest in persons over the age of 40. One out of 5 individuals who reach the age of 60 years has been said to have a colonic adenoma. The distribution of adenomas in the colon is about as follows: cecum, 10 per cent; ascending colon, 15 per cent; transverse and descending colon, 10 per cent; sigmoid colon, over 25 per cent; and rectum, over 15 per cent. The sigmoid colon and rectum are also the frequent sites of malignancy.[5] Factors particularly applicable to the sigmoid, such as the narrow lumen, stasis, and the presence of solid fecal material, are presumed to play a causative role in the formation of these neoplasms.[6]

Grossly, adenomas may be pedunculated or sessile in character and may vary in size from 1 mm. to many centimeters in length. Adenomas arising from a mucosal fold tend to develop pedicles by virtue of the peristaltic action of the intestine.[3] Truly sessile adenomas are not common; close inspection of many of these growths will actually reveal numerous individual stalks supporting the polyp. Color of an adenoma is usually determined by the richness of the blood supply, the degree of congestion, and the foci of hemorrhage, inflammation, or ulceration.[3]

The smaller adenomas usually have a regular outline, while the larger growths may be lobulated or villous. On the basis of clinical and pathologic behavior some authors have differentiated the villous adenomas from the

others,[7, 8] but present knowledge of colonic epithelial growths does not justify a complex classification. For convenience they may be classed simply as pedunculated or sessile, lobulated or villous (papillary), and malignant or benign.

Histologically, adenomas are hyperplastic, relatively mature or well-differentiated epithelial cells of uniform appearance supported by a central core of loose connective tissue. They contain stalks of varying numbers, sizes, shapes, and lengths, which differ from the normal mucosa of the colon, where a single layer of cells lines the crypts and covers the surface. Some of the cells contain a rich complement of mucus and closely resemble normal colonic epithelium, while other cells contain little or no mucus, are stratified, and exhibit a fair number of mitoses. Unless secondary infection or ulceration has occurred, no significant inflammation is found in adenomas or their supporting tissues.[2]

When pronounced dedifferentiation is present, the lesion is considered an early, preinvasive, malignant transformation, which may occur as a small focus (also known as carcinoma in situ). This reversion to the more immature or undifferentiated type of cell may be indicated by atypism, large vesicular or hyperchromatic nuclei, frequent mitoses, and excessive stratification.[2] When there is invasion through the basement membrane of the colon, the muscularis mucosae, the lesion should be considered a frank malignancy and treated as such.[8]

Any 2 of the following 3 histologic criteria—anaplasia, irregularity of architecture, and invasion[9]—are believed to constitute sufficient evidence of a carcinoma originating in adenoma.[3] Transition from adenoma to carcinoma usually occurs at the base of the growth but may also occur within or at the periphery of the tip of the adenoma. Of course, the progression of the malignant process may destroy the original adenomatous structure beyond histologic recognition.[3, 10]

Although there is a preponderance of clinical and pathologic evidence pointing to the propensity of adenomas for undergoing malignant transformation,[1-11] Colvert and Brown[12] believed, nevertheless, that rectal adenomas are either malignant initially or tend to become malignant very early; they found no evidence that malignancy tends to develop in benign adenomas over the course of time. Wangensteen, on the other hand, stated, "Experience suggests that the ordinary colic polyp becomes a cancer in approximately 2 years. Sometimes the interval is longer, sometimes shorter."[13] Atwater and Bargen believed that the benign adenoma is but "one stage in the pathogenesis of carcinoma."[4] Coller and Berry stated unequivocally that colonic polyps "are always precancerous lesions with a high chance of becoming cancerous."[11] Even in the admitted absence of clear-cut or controlled evidence, Buie stated, "All polyps of the colon are cancers (carcinomas) or will become cancers if they are not destroyed and if the patient lives long enough."[14] It is agreed that there are no microscopic characteristics that will enable the pathologist to predict a benign course for a given adenoma.[3]

PEDIATRIC ASPECTS

In children adenomas present a morphology or histologic architecture similar to that of adults except for the greater amount of connective tissue stroma.[15] The connective tissue cells in these adenomas tend to be larger and plumper and

there is generally present a greater amount of inflammatory cell infiltration. Malignant degeneration may also take place in juvenile adenomas.[16]

SYMPTOMATOLOGY

There are no pathognomonic symptoms of adenoma in adults. Usually, however, bleeding is a frequent sign, although most of these patients have concomitant anorectal lesions, such as hemorrhoids, which could cause this bleeding. Adenomas of the sigmoid are occasionally the cause of pain in the lower abdomen. In any case these symptoms generally lead the patient to seek medical advice and the comprehensive proctologic survey often results in the discovery of an adenoma. Sigmoidal polyps as the cause of abdominal pain in children were thoroughly stressed in one work.[17]

Next to bleeding, protrusion of the polyp through the anus at defecation, or at other times, as an important cause of alarm to the patient or parent of the patient. The origin of the protruding polyp may be within the reach of the examining digit or may be at some distance from the anal outlet.[17] In children it is not uncommon to find pedunculated polyps of the sigmoid protruding through the anus, and at times the location of the origin is very difficult to establish.

EXAMINATION

A comprehensive proctoscopic survey includes a bidigital rectal examination, sigmoidoscopy for a distance of 25 cm. or more, biopsy, and barium and air double-contrast roentgenography.

Digital examination and sigmoidoscopy require no comment.

In regard to biopsy, it is generally conceded that one should not rely solely on the gross appearance of the adenoma. Because, as stated, malignant transformation may take place anywhere in the adenoma (near the base, deep within the polyp, or at the tip of the body), multiple specimens of tissue should be procured from the center, the periphery, and the surrounding mucosa, including basal submucosal structures, in order to establish whether infiltration or invasion of the muscularis mucosae has occurred.[18] Whenever possible, the polyp with its pedicle and base should be removed *in toto* or in several large pieces for microscopic examination. The cold angulated biopsy forceps is ideal for the removal of even tiny adenomas, including mucosal excrescences,[19] and on occasion the electric double-loop resector may also be used.[20]

In the diagnostic examination for adenoma it is important to secure perfect air and barium double-contrast roentgen studies. Green[21] has pertinently stated that too much reliance should not be placed on radiography because many polyps are too small for roentgenographic detection.

It is now realized that the finding of a solitary rectal polyp should lead to a search for additional polyps, since many patients with single rectal polyps have additional polyps elsewhere in the colon.[12, 16, 22]

TREATMENT

Pedunculated and sessile benign adenomas and those adenomas with long and narrow pedicles that contain noninvasive malignant foci in their bodies may

be extirpated safely and effectively by means of surgical diathermy (electrothermy) or local surgical excision with a cold or electric scalpel.[2, 6, 8, 14, 17, 23-27] Surgical diathermy may be employed as an office or clinic procedure for small to moderate-sized lesions situated below the peritoneal reflection; the larger adenomas or those situated above the peritoneal reflection are treated most safely in a hospital. At the present time, we find it preferable to perform an extirpation of the entire lesion in one session with preservation of the entire specimen, or at least a great portion. Since the adoption of this policy, 2 early and small adenocarcinomas (1 in a 3 mm. adenoma) were detected promptly on microscopic examination that might otherwise, at best, have been detected only at a later date.

Mucosal excrescences and small sessile or pedunculated adenomas are now removed by the cold, angulated biopsy forceps followed by thorough desiccation of the mucosal base.[19] At times, following preliminary biopsy, these small lesions may be destroyed in situ by means of ball-tipped electrodes or means of a specially designed clamp, the curved tip of which is used to grasp the lesion lightly and is then electrically activated, thereby destroying the adenoma.[28] The larger pedunculated adenomas may be amputated at the mucosal base by means of the high frequency snare, even in the presence of a known focus or noninvasive malignancy in the body of the lesion.[6, 29] The pedicle should be examined microscopically for evidence of invasion, preferably in serial section. However, it should be pointed out that the absence of malignancy in the stalk is no assurance against metastatic invasion of the regional mesenteric lymph glands. Such rare occurrences have been observed[8, 30] and probably are effected via the lymphatic and vascular streams.

The safe use of the snare requires considerable dexterity and experience. The technique is as follows: As an optional first step, the body of the pedunculated polyp may be grasped with a special forceps[6] before the loop of snare wire is applied to the pedicle about 0.5 cm. from the mucosal base. If the grasping forceps is used, it is removed after the application of the snare wire. The stalk is gradually strangulated by slowly pulling the activated wire in the hollow of the shaft of the snare, thus amputating the tumor cleanly and efficiently. The base may then be desiccated or fulgurated lightly. The source of energy for the snare is a diathermy machine capable of delivering a steady spark about 0.5 cm. in length. In the presence of multiple adenomas, several may be removed in one sitting. When looping of the pedicle is technically impossible, the pedicle near the mucosal base may be grasped with a special clamp which is activated by applying the electric current to its handle until the crushed portion of the stalk is thoroughly coagulated. The coagulated stalk sloughs off at a later date. When the application of this clamp is also technically impossible, the electric double-loop resector may be resorted to.[20]

Certain medium-sized sessile adenomas, especially if they are located on the posterior aspect of the rectum, may be removed easily by means of the high frequency snare. The large sessile adenomas, especially if located below the peritoneal reflection, are removed with relative ease by means of the electric double-loop resector. With this instrument tumors located in inaccessible areas,

such as the upper surface of a rectal valve, can be extirpated with comparative ease, although in these instances both the tumor and the rectal valve may have to be removed. Much of the tissue so resected retains enough of the original architecture for microscopic re-examination, thus affording another early opportunity to detect malignant transformation of tissue deep in the polyp. Since the construction of this instrument, we have not found it necessary to follow the established procedure of excising large, benign, sessile adenomas of the rectum[31, 32]; until a large series of thus treated cases has accumulated, we shall continue to consider this procedure an experimental method of therapy.

The technique for the employment of the electric double-loop resector is as follows: The open loops of the instrument are placed on the neoplasm, the desired cutting current applied, and the loops are closed. (The intensity of the current should be tested preoperatively on raw meat until a considerable experience has been gained.) The maneuver is repeated until all the intraluminal projection of the tumor is resected. The base of the tumor may be desiccated at the conclusion of the resection or at a later date. Bleeding is usually prevented by the hemostatic effect of the cutting current, or it may easily be controlled by desiccation with the same instrument simply by substituting the coagulating for the cutting current.

Invasive adenomas are regarded as frank carcinomas and should be accorded appropriate radical surgical resection.

Adenomas located above the reach of the sigmoidoscope are extirpated by transabdominal colotomy when the stalk or pedicle is narrow and long.[8, 17, 31] When an adenoma elicited on roentgenography cannot be found on palpation of the colon, which sometimes occurs with a small lesion or, particularly, in obese individuals, the polyp may be located by transillumination of the gut in a darkened operating room with a specially constructed, sterile, cold light.[33] The polyp and the blood vessel of the pedicle may be visualized and distinguished from fecal particles. When this maneuver fails, the colon may be incised on the antimesenteric side and examined with the aid of a sigmoidoscope.[27] A flexible sigmoidoscope which is in the process of construction may prove useful for just such procedures.[28]

Colotomy with wide resection of the mucosal base and the submucosal structures may be employed for the removal of short-pedicled adenomas and small or medium-sized sessile adenomas in the absence of palpable lymph nodes in the corresponding area of the mesentery.[2] In some clinics frozen sections of the specimen are examined microscopically immediately after removal in order to determine whether or not invasion into the submucosa has taken place.[26] Segmental resection with end-to-end intestinal anastomosis with or without the construction of a complementary proximal vent (colostomy or cecostomy) is usually utilized for the extirpation of large sessile adenomas. Under some circumstances (poor general condition of the patient incident to old age, excessively fat mesentery obscuring the vascular pattern, and so on) the Rankin type of obstructive resection or some other type of exteriorization procedure is performed. These techniques are standard and need no description.

The principles of preoperative and postoperative care, with respect to fluid balance, nutritional requirements, anesthesia, antibiotic and sulfonamide chemotherapy, are now also well appreciated.[6] However, it should again be stressed that the sparsely absorbable sulfonamides, such as sodium phthalylsulfacetamide, are valuable, although, for unexplained reasons, even large doses of these sulfonamide drugs are ineffective in an occasional patient. For this and other reasons a combination of the sparsely absorbable sulfonamides and streptomycin should be employed. Parenthetically, the value of aureomycin as an intestinal antiseptic in intestinal surgery is in the process of investigation (Wright).

It is of interest to note that sodium phthalylsulfacetimide (thalamyd) acts not only as an intraluminal intestinal antiseptic but also diffuses in significant amounts into the deeper strata of the bowel wall. This most recently introduced sulfonamide drug is a definite aid in the preparation of the large intestine for surgical procedures.[52, 53]

The treatment of adenomas in infants and children is in no wise different from that in adults.[6]

VILLOUS (PAPILLARY) ADENOMAS

Largely through the earlier efforts of Dukes and the more recent studies of Sunderland and Binkley[7] and Scarborough and Klein,[8] the villous adenoma is now being segregated from the rest of the colonic adenomas. This lesion is regarded as an entity, for the most part, by virtue of its clinical behavior and method of growth. Probably because of long usage, the term "villous" is still preferred to "papillary" by many clinicians and pathologists.

Villous adenomas are usually found in the rectum or rectosigmoid, seldom in the colon; they occur in the older age group, the average being over 60 years old, and, in comparison to the incidence of other types of adenoma or adenocarcinoma, they are rare. These growths are solitary, of varying size, usually large and sometimes occupying the entire circumference of the bowel, and are unassociated with other rectal or colonic neoplastic lesions. Villous adenomas may be pedunculated but are usually sessile and have a wide attachment to the mucosa by means of numerous confluent, pliable, papillary stalks within the growth which present an extremely soft and spongy consistency to the examining finger. The high rate of recurrence of these lesions after treatment is a pronounced clinical feature, as well as a tendency to undergo malignant degeneration oftener than other types of colonic polyps.[7, 8] According to Sunderland and Binkley,[7] cancer may occur in any part of the growth without any special predilection for the periphery or base, while Scarborough and Klein[8] believed that malignant transformation usually begins deep in the base, often without surface evidence of its existence. Frequently, malignant degeneration may be suspected digitally on the basis of induration within the soft spongy growth. Clinically, villous adenomas occupy a position midway between benign nonvillous adenomas and adenocarcinoma.[7] Histologically, this lesion may be benign, atypical but nonmalignant, or frankly malignant. Malignancy may exist either as isolated foci of noninvasive adenocarcinoma in benign villous

adenomatous tissue or as frank invasive carcinoma retaining but small remnants of the original benign villous adenomatous architecture.

The benign villous adenoma may be removed *in toto* either by local excision or electrothermy.[6-8, 34] Because of its great malignant potentialities the extirpation of the entire lesion at the initial procedure is of utmost importance in order to avoid repeated trauma incident to therapeutic procedures. The ideal treatment aims at the complete removal of the polyps and the preservation of all or a great portion of the specimen for histologic re-examination to detect a previously missed or hidden malignancy.

Local excision with ligation of the base lends itself to the treatment of lesions that prolapse through the anus.[34] Local excision can also be effected by means of an electric scalpel.[34] When electrosurgical procedures are used, we prefer the high frequency snare whenever feasible or, when technical difficulties preclude the use of the snare, the electric double-loop resector.[2, 6] As stated elsewhere in the text, with this instrument it is possible to eradicate in a single sitting the large tumors with broad sessile attachment to the mucosa, even though these are located in certain inaccessible areas.

Villous adenomas with invasive carcinoma are accorded wide intestinal resection consistent with modern concepts of radical cancer surgery. Resection of the rectum is employed for the lesions with an "atypical" structure that cannot be removed by "local surgical excision."[7] Radical surgery is chosen because the atypical villous adenoma is such a treacherous lesion.[34]

Irradiation, roentgen or radium, has limited, if any, usefulness in the treatment of villous adenomas.[34]

FAMILIAL ADENOMATOSIS

Colon.—Familial adenomatosis, or polyposis, was first reported by Menzel in 1721 and was accurately described by Virchow in 1863. It is regarded as a heredofamilial, and perhaps congenital, entity, behaving as a mendelian recessive transmitted by genes.[35] Apparently, an inherited factor, quite similar to amaurotic idiocy or hereditary optic atrophy,[36] is greatly responsible for the development of adenomatosis, while a precipitating cause plays a smaller role. Malignant transformation of one or more of these polyps nearly always occurs during the early decades of life. In many cases members of these families who escape adenomatosis develop rectal or colonic carcinomas several years earlier than the average person.

No known case of this lesion at birth has thus far been reported,[37] although McKenney believed familial adenomatosis may exist at birth.[38] Recently, the occurrence of this disease in an infant 4 months old[38a] and in 2 infants, each 18 months old, was reported.[39] (See Familial Adenomatosis of the Entire Gastrointestinal Tract, to be discussed later.)

The entire large intestine may be studded with adenomas of varying size, and even the vermiform appendix may be affected.[40]

Modern treatment has become increasingly more radical.[26] Of historic interest is the fact that ileosigmoidostomy as a primary operation was performed

by Lilienthal[41] on March 6, 1900, and was followed by a subtotal colectomy on June 15, 1900. This operation, with the addition of fulguration of the rectal polyps by proctoscopy, is still being advocated.[35, 42] Guptill[35] endorsed the procedure of primary fulguration of adenomas of the lower rectum, anastomosis of the ileum to the rectum, and a two-stage colectomy (plus careful periodic follow-up observation). He particularly stressed the necessity of ileal anastomosis to the lower portion of the rectum (8 cm. from the anal orifice) so that subsequent endoscopic observation could be carried out. This is an important point, for I have observed 3 patients with successful anastomoses of the ileum to the low sigmoid in whom neither the site of the anastomosis nor the immediate surrounding areas could be visualized postoperatively with a sigmoidoscope 25 cm. long. Dixon and Benson[39] first performed an ileorectosigmoidostomy, using an open isoperistaltic, side-to-side anastomosis with excision of the colonic polyps situated near the anastomosis. At a subsequent operation a subtotal colectomy is performed, followed by transproctoscopic fulguration of the polyps of the rectum and rectosigmoid. Buie[14] preferred this sequence of operations, because he has seen patients succumb to subtotal colectomy after the successful, but energy- and time-consuming, process of fulguration of the adenomas of the rectum and rectosigmoid.

Total colectomy and proctectomy are usually reserved for complicating cancer of the rectum or when the adenomas are so numerous that they cannot be removed successfully by surgical diathermy through the endoscope. At times, proctectomy is indicated for uncontrollable hemorrhage resulting from recurrent adenomas after colectomy. Having noted instances of malignancy following ileoproctostomy and subtotal colectomy, Cattell[26] held that the operation of choice is the two-stage permanent ileostomy followed by total colectomy including abdominoperineal resection of the rectum. The new techniques of anal ileostomy with preservation of sphincter control[43, 44] will undoubtedly influence the adoption of total colectomy as the treatment of choice for eradication of familial adenomatosis.

Roentgen or radium irradiation may afford symptomatic relief[45] and may, therefore, be employed in the occasional patient who refuses surgery. It should be remembered, however, that these tumors are usually radioresistant and that progression of the lesion following radiation therapy has been observed; furthermore, one instance of secondary malignancy is known to have occurred following irradiation.

Entire Gastrointestinal Tract.—The occurrence of familial adenomatosis of the entire gastrointestinal tract has been observed and discussed in detail by Ravitch.[46]

ADENOMAS AND INFLAMMATORY DISEASE

In long-standing ulcerative colitis one may observe inflammatory mucosal polypoid projections (a sort of hypertrophy of the remaining fragments of the mucosa which were named pseudopolyps by Woodward in 1881), true adenomas, or carcinoma. The occasional adenoma observed in association with ulcerative colitis or amebic dysentery is managed in the same manner as adenomas in un-

inflamed colons.[6] However, multiple adenomas found in association with chronic ulcerative colitis are best eradicated by total colectomy because of their alleged ability to undergo malignant changes.[8, 47] Some authors believe that pseudopolyps seen in chronic ulcerative colitis may transform into the intermediary adenoma and finally into frank carcinoma.[47, 48] This view has not found support in the pathologic studies of other authors.[1, 3, 49, 50] However, malignant foci of precancerous epithelial hyperplasia may develop during regeneration of the mucosal epithelium which continues despite repeated ulcerations.[50] This problem is under intensive study at the present time.[51]

FOLLOW-UP OBSERVATION

It is now generally agreed[8, 26] that periodic sigmoidoscopic and roentgenographic studies should be made for an indefinite period of time in all patients in whom adenomas have been extirpated for the purpose of detecting new or recurrent lesions at the earliest possible moment. The fact that individuals afflicted with adenomas have a pronounced tendency to develop new and/or recurrent polyps with the passage of time makes this careful follow-up observation a sound procedural policy.

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CARCINOMA OF THE COLON PERFORATING ONTO THE ANTERIOR ABDOMINAL WALL

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CARCINOMA is the most commonly observed tumor of the colon. It accounts for about 7 per cent of all cancers.[6] It spreads by (1) direct extension, (2) invasion of lymph vessels and nodes, (3) the venous system, and (4) transperitoneal implantation.[9, 14] Attachment of the affected portion of the colon to adjacent structures is important from the standpoints of both resectability and prognosis.[15] Such attachment may be due to actual malignant invasion or to inflammation.[18, 20]

The present study is concerned with 30 cases of primary carcinoma of the colon that had perforated onto the anterior abdominal wall in which resections were performed with the hope of cure. Twelve of the patients had undergone exploratory laparotomy or drainage of an abscess of the abdominal wall elsewhere, but the others had not had previous operations related to the colonic lesion.

Early reports of cases of carcinoma of the colon involving the abdominal wall were presented by Thurnam, Hobson, Hill, Harley, and Bidwell. In 1925, Menninger and Holder described a case of carcinoma of the sigmoid which had ruptured into the anterior abdominal wall. Bloodgood recalled a similar case, except that in this instance the neoplasm originated in the cecum. In 1944, Gratiot and Nunes reported a case of carcinoma of the sigmoid complicated by perforation, abscess, and a fistulous tract to the abdominal wall.

In 1947, Brunschwig gave detailed reports of 13 cases of intra-abdominal cancer invading the anterior abdominal wall, 8 of which originated in the colon. Resection of all macroscopic neoplastic tissue was performed in one stage. The author noted that some of the best results were obtained in cases in which the primary growth was colonic, especially in the absence of hepatic metastasis. Even in the absence of absolute cure, palliation and prolonged survival might follow extensive resection in such instances.

MATERIALS AND METHODS

From 1906 through October, 1946, some type of surgical procedure for carcinoma of the colon was performed on 4,947 patients at the Mayo Clinic. Cancer of the rectum was not included. Of this number, involvement of the anterior abdominal wall was found in 121 instances (2.4 per cent). However, only 30 of the 121 cases fell within the limits of this study.

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The remaining 91 cases were rejected for one or more of the following reasons: (1) The involvement of the abdominal wall represented recurrence; in some instances this occurred at the site of the colonic stoma which was formed at the time of colostomy. (2) Removal of the growth was found to be impossible. (3) Resection was performed, but considered merely palliative. (4) The lesion involved a sizeable portion of the stomach. (5) Metastasis to the liver was present. (6) The surgical specimen was not available (1 case). There were, then, 30 cases in which resection had been performed which showed involvement of the anterior abdominal wall at the time of the operation, but in which it was considered that all malignant tissue had been removed.

The pathologic material consisted entirely of surgical specimens, which had been preserved in 10 per cent formalin. The lesion was measured, and its direction of growth (ulcerative or polypoid) was noted. It was inspected further for abscesses, gross mucus, lymph nodes, and tissue adherent to the serosal surface of the bowel. Several blocks of tissue were removed from selected areas of each specimen for microscopic study. These blocks were placed in a fresh solution of 10 per cent formalin and later sectioned on a freezing microtome. The sections were stained with hematoxylin and eosin and mounted permanently on glass slides.

The neoplasms were graded 1 to 4, according to the method of Broders. They also were typed, employing a modification of Dukes' classification of cancer of the rectum.[7] Type A was used to indicate confinement of the malignancy to the mucosa and submucosa of the bowel; type B, spread of the disease to the muscularis propria or visceral peritoneum; and type C, involvement of lymph nodes.

The clinical history and the follow-up correspondence in all cases were reviewed.

CLINICAL AND SURGICAL FINDINGS

There were 19 males and 11 females. The average age was 49 years. The most common symptoms were abdominal pain, loss of weight, change of habits concerning bowels, and a mass in the abdomen. The type of pain was not characteristic of perforation. Of the 30 patients, 11 had noted a mass in the abdomen for periods varying from 1 week to 6 months. The average duration of all symptoms was 10.4 months.

Physical examination of the abdomen revealed a palpable mass in 90 per cent of the cases. In one-half of them, the mass was said to be fixed, but attachment to the abdominal wall was suggested by the examiner in 3 instances only. Purulent drainage from a sinus tract in the right lower quadrant of the abdomen was encountered in 3 cases.

The value for hemoglobin of three-fourths of the patients was less than 12 Gm. per 100 c.c. of blood. The leucocyte count had been obtained in 29 cases, and in 14 it was more than 10,000 cells per cubic millimeter of blood. The elevation in the number of leucocytes was not great, however, the highest count being 16,600 cells.

Records of roentgenologic studies of the colon were available in 24 of 30 cases. The roentgenologist's diagnosis was carcinoma of the colon in 17 cases (70.8 per cent). The diagnosis in the remaining 7 cases included perforating lesion, filling defect, obstructing lesion, and pericecal mass.

Twelve of the 30 patients had undergone some type of operation related to carcinoma of the colon before coming to the clinic. The various surgical procedures, performed from 1 month to 28 months prior to resection, included exploratory laparotomy, incision and drainage of an abdominal abscess, ileocolostomy, appendectomy, and laparotomies for the removal of adhesions and for acute intussusception. In addition, 1 patient was said to have had a mass in the colon partially removed.

The surgeon recorded the locations of the carcinomas as follows: cecum, in 12 cases; ascending colon, 4; hepatic flexure, 3; transverse colon, 1; splenic flexure, 1; descending colon, 5; sigmoid colon, 4. All of the growths were found to be adherent to the abdominal wall, and in 3 instances there were sinuses extending to its surface.

A one-stage procedure including ileocolostomy and removal of the right one-half of the colon was performed in 12 of the 30 cases. Obstructive resection (Rankin) was employed in 8 cases. A two-stage procedure, consisting of ileocolostomy first and right hemicolectomy later, was accomplished in 5 instances. Resection of the lesion and primary anastomosis of the colon was carried out in 3 cases. A Mikulicz type of operation was performed in the remaining 2 cases.

In addition, the following procedures were necessary in 1 case each: curettage of a sinus tract, incision and drainage of an abscess, temporary ileostomy, temporary transverse colostomy, and cautery to the abdominal wall.

In 27 of the 30 cases a portion of the abdominal wall was resected along with the growth. The diseased segment of colon was dissected free from the abdominal parietes in the other 3 cases. Two of these 3 patients were later found to have a recurrent malignant growth in the abdominal wall. In the other case, a specimen was removed from the adherent wall which was found to show evidence of inflammation.

PATHOLOGIC FEATURES

The area of the growth, as it involved the mucosa of the colon, was determined. It was felt that the thickness of the mass should be disregarded, because it was impossible to know how much of it was the result of inflammation. The average area of the 30 specimens was 57.2 sq. cm. In general, then, the lesions could be described as large.

In regard to the direction of growth, 21 of the lesions (70 per cent) were found to be of the ulcerative type. The carcinoma was polypoid in the remaining 9 cases (30 per cent). All of the growths were perforating in that they were adherent to adjacent structures.

Five of the lesions were grade 1, 16 were grade 2, 6 were grade 3, and 3 were grade 4. Thus, it is seen that neoplasms of grades 1 and 2 occurred in 70 per cent of the cases, and growths of grades 3 and 4 occurred in 30 per cent.

One carcinoma of grade 4 was of the scirrhous variety, and it also showed perineural spread along the myenteric plexus. The patient was a girl 16 years of age.

The lesions were classified further as type A, B, or C, according to a modification of Dukes' classification of cancer of the rectum, as explained previously. As might be anticipated, none of the lesions were of type A. In 13 cases (43.3 per cent) peritoneal involvement was evident but there was no nodal involvement (type B). In the remaining 17 cases (56.7 per cent), spread of the carcinoma to regional lymph nodes was present (type C). Sections from 2 specimens revealed plugging of the lymphatics by carcinomatous cells.

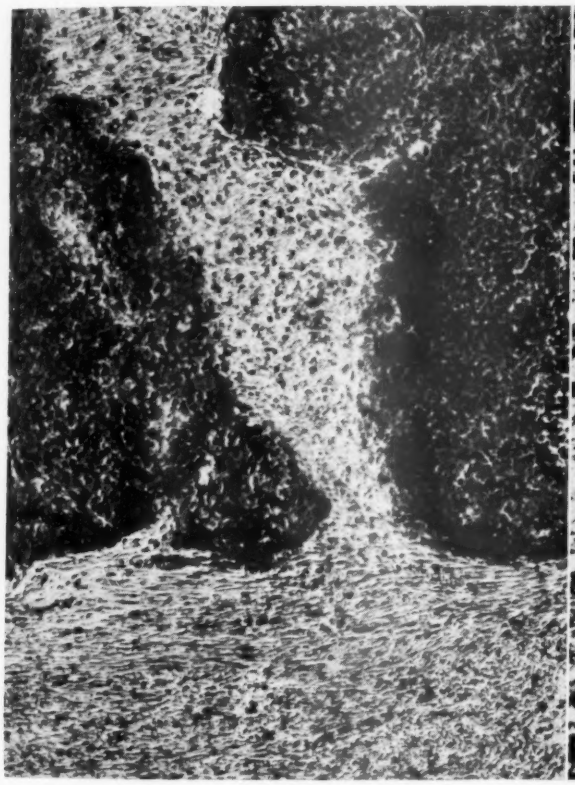

Fig. 1.

Fig. 2.

Fig. 1.—Adenocarcinoma, grade 4, involving fascia of the abdominal wall (hematoxylin and eosin, ×100).

Fig. 2.—Adenocarcinoma, grade 3, which penetrated an operative scar on the anterior abdominal wall (hematoxylin and eosin, ×100).

It is interesting that microscopic examination of the growths showed them to be of the mucous variety in 11 cases (36.7 per cent). This is a much higher incidence than would be expected. In 6 of these 11 cases of mucous cancer, carcinomatous lesions had invaded the abdominal wall.

Microscopic study of sections from the adherent portion of the abdominal wall revealed inflammation in all cases. Evidence of definite formation of abscesses was present in 12 cases (40 per cent). Actual invasion of the ab-

dominal wall by carcinomatous cells was discovered in only 12 cases (40 per cent) (Figs. 1 and 2). In 18 of the 30 cases, therefore, the only changes which were found in the excised section of the abdominal wall were those related to inflammation. In 5 of the 18 cases, however, carcinomatous lesions are known to have developed in the abdominal wall subsequently. Malignant invasion of the wall of a sinus tract was evident in 2 of 3 cases (Fig. 3).

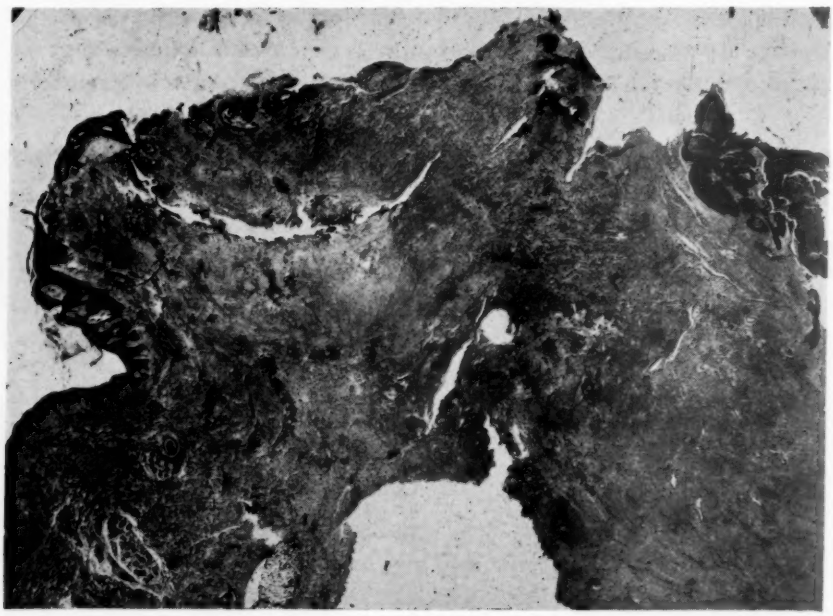

Fig. 3.—Portion of the wall of a sinus tract leading from the cecum to the surface of the abdomen. Carcinomatous cells may be seen along the top of the section, while the skin is evident at the left (hematoxylin and eosin, ×8).

RESULTS

Sixteen of the 30 patients (53.3 per cent) are known to have died. Three died in the hospital after operation, a hospital mortality rate of 10 per cent. Another patient, who had hypertensive heart disease, was found dead 5 months after operation, and it seems probable that in this case death was the result of cardiac failure. The average duration of life of the remaining 12 patients after operation was 19.7 months.

In 7 of the 12 cases (58.3 per cent) carcinomatous lesions recurred in the abdominal wall prior to death. The earliest recurrence was discovered 4 months postoperatively, while the latest was 3½ years after surgical intervention. Actual involvement of the abdominal parietes by malignant lesions at the time of resection was found in 6 of the 16 cases.

Fourteen of the 30 patients (46.7 per cent) were alive when the last inquiry was made (Table I). Of this group, 6 patients had had actual carcinomatous invasion of the abdominal wall at the time of resection. One man was alive and well 10 years after operation. A man, 49 years of age, underwent right hemicolectomy for carcinoma of the cecum. Nineteen months later, wide

excision of a recurrent lesion on the abdominal wall was performed (Fig. 4), and the patient was alive and well 10½ years after the first operation.

Seventeen patients of the group of 30 were operated upon 5 or more years before our study was made. Two patients died in the immediate postoperative period. The other 15 patients were able to leave the hospital, and 3 of them lived 5 years or longer. Only 1 patient who survived 5 or more years had demonstrable invasion of the abdominal wall by a malignant lesion at the time of resection. In another case, however, demonstrable involvement was lacking at the first operation, but a recurrent lesion had developed in the abdominal wall 19 months later and was excised at that time.

Nineteen patients have survived 3 or more years since operation. A 3 year survival rate of 36.8 per cent is obtained for the group.

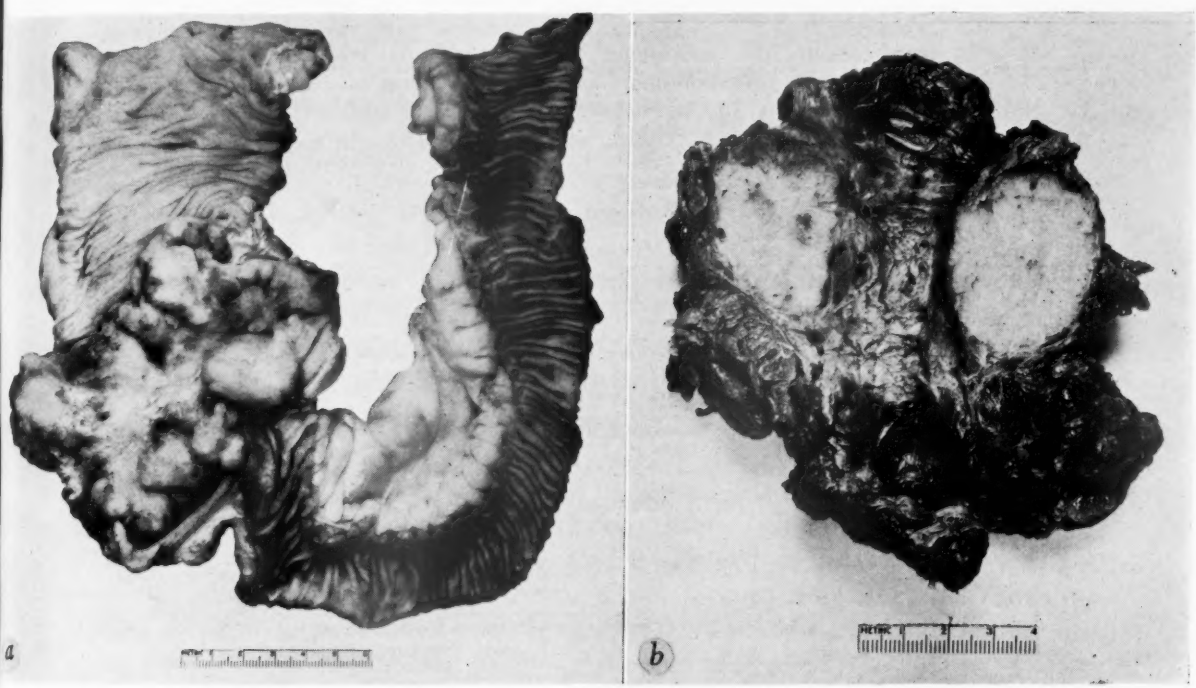

Fig. 4.—*a*, Gross specimen of a large carcinoma of the cecum. The cecum was firmly attached to the parietal peritoneum of the anterior abdominal wall, but microscopic sections showed only inflammatory involvement of the latter structure. *b*, Recurrent carcinoma of the anterior abdominal wall (same patient), excised 20 months after the first operation. The patient was alive and well 10½ years after the initial resection.

Seven patients have survived 2 to 3 years. Recurrences involving the abdominal wall are known to have occurred in 2 of the 7 cases, appearing 6 months after resection in 1 case and 8 months postoperatively in the other. Another patient apparently had hepatic metastasis 22 months after resection for carcinoma of the sigmoid, although there was no recurrence in the abdominal wall.

In the entire series of 30 cases, recurrence of carcinoma in the abdominal wall occurred in 10 (33 per cent). At the time of the last inquiry 7 of the 10 patients were dead. Excision of a recurrent lesion in the abdominal wall was

carried out in only 1 case, and this patient was well 9 years after operation. Six patients received roentgen therapy for recurrent lesions, apparently without benefit.

COMMENT

Carcinoma of the colon may be said to be perforating when malignant cells have penetrated the muscularis propria and invaded the visceral peritoneum. Although perforation of the wall of the bowel may be acute, it is more often chronic.[20] The process is always associated with inflammation; abscesses may be formed, and this occurred in 40 per cent of our cases. The involved segment of the colon may become adherent to adjacent organs.

TABLE I. SUMMARY OF 14 PATIENTS ALIVE AT LAST REPORT

AGE, SEX	CARCINOMA: LOCATION,* TYPE, GRADE	OPERATIVE PROCEDURE	STRUCTURE REMOVED; CANCEROUS INVOLVEMENT OF ABDOMINAL WALL	SUBSEQUENT COURSE FROM INITIAL RESECTION
58 M	Hepatic flexure, grade 3 (mucous)	Ileocolostomy and right colectomy (two-stage)	Full thickness abdominal wall; positive	Well, 10 years
49 M	Cecum, grade 2	Right colectomy (temporary ileostomy)	Parietal peritoneum; negative	Excision of recurrent lesion abdominal wall 19 months; well, 10½ years
43 M	Sigmoid colon, grade 2	Resection and anastomosis	Parietal peritoneum, left vas deferens; negative	Hepatic metastasis, 22 months
72 F	Cecum, grade 1 (mucous)	Ileocolostomy and right colectomy (two-stage)	Lesion dissected from abdominal wall; negative	Recurrence in abdominal wall, 6 months
31 M	Cecum, grade 3	Right colectomy	Posterior fascia and part of rectus muscle; positive	Recurrence in abdominal wall, 8 months
57 M	Cecum, grade 2	Right colectomy	Sinus tract to abdominal wall; positive	Radium and roentgen therapy to abdominal wall; well, 2 years
70 M	Ascending colon, grade 2	Right colectomy	Part of transversalis and iliopsoas muscle; positive	Well, 2⅔ years
40 M	Sigmoid colon, grade 2 (mucous)	Exteriorization (clamp method)	Muscle abdominal wall; positive	Well, 3 years, 5 months
49 M	Cecum, grade 1 (mucous)	Right colectomy	Parietal peritoneum; negative	Well, 3 years, 1 month
74 F	Ascending colon, grade 2	Right colectomy	Muscle, abdominal wall; negative	Well, 2⅔ years
34 M	Transverse colon, grade 2	Resection and anastomosis	Parietal peritoneum, transversalis fascia; fistula into bladder; negative	Well, 3 years
56 M	Cecum, grade 1 (mucous)	Right colectomy	Fascia and muscle; positive	Well, 2⅙ years
58 F	Hepatic flexure, grade 3	Right colectomy	Fascia, muscle, portion of stomach; negative	Well, 3½ years
26 F	Descending colon, grade 2 (mucous)	Exteriorization (clamp method)	Parietal peritoneum; negative	Well, 5⅓ years

*Note preponderance of lesions in right portion of colon.

Involvement of the anterior abdominal wall by carcinoma of the colon, including both primary and recurrent growths, occurred in 2.44 per cent of the cases reviewed. Gilchrist and David found it necessary to resect a portion of the abdominal wall in 4 of 200 cases. Mayo and Schlicke reported involvement of the abdominal wall in 1.5 per cent of 334 cases of carcinoma of the colon and rectum, all of which were studied at necropsy. Sugarbaker removed carcinomas of the colon and rectum in 147 cases and found involvement of the anterior abdominal wall in 4 of them (2.7 per cent).

The presence of a fixed mass in the abdomen, plus characteristic roentgenologic findings when a barium enema is used, should suggest perforation of the colonic neoplasm onto the abdominal wall.

That portion of the anterior abdominal wall which is firmly adherent to the diseased segment of colon should be removed, if possible. Actual malignant invasion of this adherent tissue is present in only 40 per cent of the resectable cases.

There are 2 reasons which might be suggested for the preponderance of lesions in the right portion of the colon, which is a reversal of the usual anatomic distribution. In the first place, the mobility of the cecum is probably an important factor, in that it permits this portion of the bowel to come in contact with the anterior abdominal wall. Secondly, consideration must be given to the fact that carcinomas in the right portion of the colon tend to be larger than those occurring in the left portion. As might be anticipated, the incidence of actual carcinomatous invasion of the abdominal wall increased in direct relationship to the grade of the malignant lesion.

In 11 of the 30 cases the neoplasms were of the mucous variety. Rankin found approximately 1 of 7 carcinomas of the colon to be of the colloid or mucoid type. He stated that this type of malignant lesion was slow growing and that it usually spread by direct extension. Cole and associates stated that colloid carcinoma of the colon is rare, that it occurs particularly in the cecum, and that it is likely to lead to perforation and formation of abscesses. In 8 of our 11 cases of mucous cancer, the lesions occurred in the right portion of the colon and 6 of these were in the cecum. Abscesses were present in 4 cases. Willis stated that especially in cases of gelatinous carcinomas of the stomach or intestine the area of peritoneum affected by the primary tumors might be extensive.

The abdominal wall had been invaded by the carcinomatous lesion in 6 of the 11 cases. Recurrent malignant lesions are known to have developed in the abdominal parietes of 5 of the 11 patients. Six of the patients who had mucous cancers were alive at the time of the last report (Table I).

In 50 per cent of his series of cases in which lesions were removed Sugarbaker found actual extension of carcinoma into the adjacent structures. In 3 of 4 cases in which a portion of the anterior abdominal wall was removed, malignant lesions had invaded the structure. Carcinoma was discovered in the abdominal wall in 40 per cent of the 30 cases reported herein. Rankin and Broders expressed the opinion that fixation of a carcinoma of the colon to adjacent structures was often due to inflammation, rather than to direct extension of the malignant lesion. Willis stated that the dermis, being compact tissue,

tends to resist neoplastic invasion, while direct invasion of skeletal muscle is frequently seen.

Eleven patients apparently were well when last heard from. In each case, 2 or more years had elapsed since operation. It is encouraging to note that of the 11 patients, 5 had actual carcinomatous involvement of the abdominal wall at the time of removal of the primary growth in the colon (Table I). It is not so encouraging, however, to note that among the patients recovering from resection, only 20 per cent survived 5 or more years.

Gilchrist and David removed a portion of the abdominal wall, along with a carcinoma of the colon, in 4 cases. Three of 4 patients were alive and well 5 to 10 years later, while 1 died of hepatic metastasis.

SUMMARY

From 1906 through October, 1946, involvement of the anterior abdominal wall occurred in 2.44 per cent of the cases of carcinoma of the colon at the Mayo Clinic. A discussion is presented of 30 cases of primary carcinoma of the colon perforating onto the anterior abdominal wall in which resection was done with a view to cure.

The average age of the 30 patients was 49 years. Abdominal pain and loss of weight were the commonest complaints. More than one-third of the patients were aware of a mass in the abdomen. The average duration of symptoms was 10.4 months.

The examiner found an abdominal mass in 90 per cent of the cases. There was a sinus tract in the right lower quadrant in 3 cases. In the laboratory, roentgenologic study of the colon with the use of a barium enema proved to be the most revealing diagnostic procedure.

Removal of the lesion was accomplished in a one-stage procedure in 77 per cent of the cases, and a portion of the adherent abdominal wall was removed in 90 per cent. Nineteen of the growths originated in the right portion of the colon, 1 in the transverse colon, and 10 in the left portion of the colon.

Seventy per cent of the carcinomas were of the ulcerative type, and 30 per cent were polypoid. The average area of the specimens was 57 sq. cm. The degree of malignancy was graded 1 or 2 in 70 per cent of the cases and 3 or 4 in 30 per cent. All of the growths had penetrated to the overlying visceral peritoneum, and 57 per cent of them had spread to regional lymph nodes. The carcinoma was mucous in character in 37 per cent of the specimens, and more than one-half of these revealed invasion of the abdominal wall. There was demonstrable spread of the cancer into the resected portion of the abdominal parietes in 40 per cent of the entire series.

Recurrent carcinoma in the abdominal wall is known to have developed in one-third of the cases. Of those patients who recovered from resection, 20 per cent survived 5 or more years. Eleven patients were alive and well 2 or more years after operation.

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THE PROBLEM OF DIAGNOSIS AT THE TIME OF OPERATION IN TUMORS OF THE HEAD OF THE PANCREAS

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SINCE 1935, when Whipple[1] made his brilliant contribution, there has been a widespread interest in pancreaticoduodenal resection in the treatment of malignant tumors of the head of the pancreas, the ampulla of Vater, and the periampullary area. The results reported to date are rather disheartening. The hospital mortality rate, although it has shown progressive improvement, still is formidable, ranging from Cattell's[2] reported rate of 14.8 per cent in 56 cases, to that reported in a series of 32 cases at the Presbyterian Hospital in New York, a 53 per cent mortality.[4] The average hospital mortality rate among those resections reported in the literature since 1942 is approximately 30 per cent.[2-12] The 5 year survival rate is even more discouraging. Parsons[12] has reported a 6 year survivor with evidence of metastases, in whom the primary tumor was a nonsecretory islet-cell carcinoma. Other than this there have been no 5 year survivors when the primary tumor was in the head of the pancreas.

An additional disturbing element in the management of a mass in the head of the pancreas is the well-known difficulty of obtaining a tissue diagnosis of malignancy at the time of laparotomy. A microscopic confirmation of the diagnosis is important, for chronic pancreatitis may cause an obstructive jaundice which is practially indistinguishable from that caused by carcinoma of the head of the pancreas. In 1923 Hartman[13] reported 26 cases with obstructive jaundice in which a hard mass was felt in the head of the pancreas. At autopsy it was found that 21 of these cases had carcinoma, but the remaining 5 had only chronic pancreatitis. Walters[14] reported in 1932 that 15 per cent out of 113 patients with obstructive jaundice due to a mass in the head of the pancreas survived 5 years or longer following a palliative shunt operation. He attributed their longevity to the presence of chronic pancreatitis rather than a carcinoma in the head of the pancreas. Behrend and Behrend[15] reported a series of 10 cases of chronic pancreatitis, in 7 of which jaundice was present at the time of operation. In 2 of the cases a biopsy was done and a histologic diagnosis of chronic pancreatitis was made. The other 8 cases all survived 5 years or longer following a biliary-intestinal anastomosis and the authors assumed that the hard mass in the head of the pancreas was inflammatory rather than neoplastic in origin. An occasional report in the literature also mentions the resection of benign lesions which have been mistaken for carcinoma. Orr[7] de-

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scribed 1 such instance in his series of 9 cases reported in 1945. In a series of 30 resections, Cattell[2] reported 3 cases in which chronic pancreatitis was mistaken for a malignant lesion.

It is the purpose of this paper to report 4 cases which have been seen within 19 months* at this hospital, all of which presented a diagnostic difficulty at the operating table.

CASE REPORTS

CASE 1.—W. S. (R-23 433), a 60-year-old white man, was admitted to the Medical Service at the Albuquerque Veterans Hospital on April 23, 1947, with the chief complaint of jaundice of 10 days' duration, together with the passage of clay-colored stools and a dark "brown" urine. On admission the patient stated that for 2 months previously he had had anorexia and that he would go to the table desiring to eat but would fill up after eating only a small amount. Ten days prior to admission he developed jaundice. For 8 days prior to admission he complained of passing 4 to 5 soft, clay-colored stools daily. He denied vomiting, abdominal pain, chills, or fever. The past history revealed that the patient had had an x-ray diagnosis at this hospital of duodenal ulcer 39 months prior to the present admission. On a medical regime the ulcer symptoms had subsided and the patient was well from 1944 to the time of the present illness. He had gained 40 pounds and was asymptomatic during this interval.

Physical Examination.—On admission, physical examination revealed a well-nourished white man with no evidence of recent weight loss. There was moderate jaundice of the skin and sclerae. The vital signs were normal. Other positive physical findings were limited to the abdomen. There was no abdominal distention, ascites, nor dilated superficial veins. The liver edge was palpable 2½ cm. below the costal margin, the edge being smooth and nontender. No other abdominal viscera nor masses could be felt.

Laboratory Studies.—Hemogram and urine were normal save that the latter was positive for bile, and merely a trace of urobilinogen was found. A trace of bile was found in the stool, as well as a trace of urobilinogen. A gastric analysis revealed 60 degrees of free acid after histamine and 100 degrees of total acid. Liver function tests revealed a negative cephalin flocculation test, and the serum proteins were within normal limits with a normal albumin/globulin ratio. A positive direct van den Bergh reaction was found. Serum bilirubin was 30 mg. per cent. A red cell fragility test was normal. The gastrointestinal series on May 7, 1947, revealed no evidence of organic pathologic changes in the esophagus, stomach, or duodenum.

Course in the Hospital.—On May 14, 1947, a surgical consultation was requested and it was recommended that the patient be subjected to exploratory laparotomy, with a preoperative diagnosis of obstrucive jaundice, probably due to malignancy in the head of the pancreas. On May 21, 1947, a laparotomy was carried out by a visiting surgeon. The gall bladder was found to be thin walled and markedly dilated. It contained clear white bile without evidence of calculi. The common duct was enlarged to approximately 3 cm. in diameter and contained no stones. A hard tumor mass was felt in the head of the pancreas, measuring about 7 cm. in diameter. The operator felt that the mass represented a carcinoma of the head of the pancreas and no biopsy was obtained. A radical pancreaticoduodenectomy was carried out in 1 stage. After a stormy postoperative course the patient expired on the ninth postoperative day with dehiscence of the suture line between the pancreas and jejunum.

The pathologic description† of the surgical specimen is as follows: The pancreas disclosed extensive replacement of the acinar parenchyma by fibrous tissue. The glandular parenchyma persisted only in the form of isolated islands of acinar tissue. Areas of moderate

*During this same period 1 pancreaticoduodenectomy was carried out for a tumor of the distal common duct, with a frozen section diagnosis of adenocarcinoma. This patient is living, without evidence of recurrence, 12 months postoperatively.

†By Dr. Sidney Marks, Pathologist.

lymphocytic infiltration were present on the background of the fibrous tissue. The islands of Langerhans were preserved, usually existing in an isolated state. Moderate dilatation of the pancreatic ducts was noted. Sections of the duodenum revealed partial replacement of the muscular layer by fibrous tissue. In these areas an extensive infiltration of lymphocytes was noted. The mucosa overlying the fibrosis and inflammation was intact. Diagnosis were: (1) chronic pancreatitis; (2) moderate dilatation of the pancreatic ducts; (3) chronic inflammation and fibrosis of the duodenum.

An autopsy was performed on the patient, with the following pathologic findings: On gross examination, the body and tail of the pancreas had a dull yellowish appearance on the cut surface and the lobular pattern was not distinctly present. The thickness of the parenchyma appeared to be diminished. Only a few small, brightly yellow areas were apparent, these being present in the roughened region of excision.

On microscopic examination the pancreas showed almost complete replacement of the acinar parenchyma by fibrous tissue. The islands of Langerhans were completely surrounded by fibrous tissue. Lymphocytic infiltration was marked. There was a mild degree of fat necrosis in the peripancreatic fat. There was no evidence of carcinoma.

Comment.—This case represents a situation in which a competent surgeon felt, on the basis of gross examination alone, that the presence of a mass in the head of the pancreas represented a carcinoma causing obstructive jaundice. With this gross diagnosis a radical operation was undertaken with an operative mortality on the ninth postoperative day. This patient's jaundice which was caused by chronic pancreatitis could have been relieved by a less radical procedure, that is a cholecystoenterostomy, and probably this fatality could have been prevented.

CASE 2.—E. P. (R-27 644), a 56-year-old white man, was admitted to the Albuquerque Veterans Hospital on Dec. 4, 1948, with a chief complaint of intermittent upper abdominal pain of 2 years' duration. In November, 1946, the patient had had an attack of upper abdominal pain associated with jaundice and was subjected to exploratory laparotomy at another hospital. The laboratory data from this hospital is not available but a conversation with the operating surgeon revealed that the man had obstructive jaundice and was found to have a large hard nodular mass in the head of the pancreas, which on gross examination and without biopsy was deemed to be an inoperable carcinoma of the head of the pancreas. The abdomen was closed without further ado and the patient was told that he had a life expectancy up to 6 months. On his return home the patient noted recurrent bouts of upper abdominal pain associated with nausea and vomiting but without jaundice, which had subsided following the laparotomy. During the 2 year interval between the first hospitalization and admission to this hospital the patient gained 10 pounds in weight.

Physical Examination.—The patient was a well-nourished white man without evidence of jaundice. Positive physical findings were limited to the abdomen, which was flat and contained a well-healed right upper rectus scar, in the upper angle of which there was a palpable mass roughly 8 by 10 cm. which was quite tender and which moved with respiration. This mass appeared to be continuous with a palpable liver edge which could be felt 2 cm. below the costal margin. The liver edge was smooth and nontender.

Laboratory Studies.—A normal hemogram was present and the sedimentation rate was 10 mm. per 1 hour. (Westergren). The urine was negative save for an occasional hyaline cast. The icterus index was 10 units. Bile was present in the stool and no occult blood was discovered. The bromsulfalein (5 mg. per kilogram) test revealed no dye retention in 45 minutes. The total serum proteins measured 6.8 Gm. per cent, with a normal albumin/globulin ratio. An upper gastrointestinal series was negative. An oral cholecystogram revealed a nonfunctioning gall bladder with a large circular area of calcification in the region of the gall bladder.

Course in the Hospital.—On Dec. 14, 1948, an exploratory operation was performed through a transverse incision and the patient was found to have a pericholecystic abscess with a large solitary stone in the gall bladder. Palpation in the region of the head of the pancreas revealed no evidence of tumor and the liver was free of metastases. Postoperatively the patient did well and was discharged with a healed wound on Jan. 4, 1949.

Comment.—This patient, on the basis of a gross diagnosis at the time of laparotomy in 1946, was told that he had a carcinoma of the head of the pancreas which would cause his death in about 6 months. The obvious course of events following this laparotomy tends to underline the error of this gross examination. It is entirely likely with the later evidence of biliary tract disease that this man had a chronic cholecystitis with concomitant pancreatitis at the time of the first laparotomy.

Case 3.—R. W. (R-26 758), a 52-year-old white man, was admitted to the Albuquerque Veterans Hospital on April 12, 1948, with chief complaints of back pain and jaundice of 3 weeks' duration. The patient was well until November, 1947, when he noted pain in the back in the lower thoracic region. This pain was first intermittent but later became steady and persisted until admission. There was no radiation of pain nor was there history of trauma. Three weeks prior to admission the patient noted clay-colored stools and shortly thereafter he noted that the urine was dark in color. There was no nausea, vomiting, chills, or fever. There was a weight loss of 20 pounds in the past 4 months.

Physical Examination.—Patient was a well-nourished male with deep jaundice. Other positive physical findings were limited to the abdomen. The liver edge was palpable 1 finger-breadth below the right costal margin. It was firm, smooth and nontender. An enlarged gall bladder could be felt. There was no evidence of tenderness in this region. There were no dilated abdominal veins. There was no evidence of ascites.

Laboratory Studies.—Hemogram was normal. Urine contained a trace of albumin, 1 to 3 white blood cells, and an occasional hyaline cast. Bile was present in the urine. Cephalin flocculation was 2 plus, thymol turbidity 2 units, and the serum bilirubin was 8.7 mg. per cent. The van den Bergh test gave a prompt direct reaction. Prothrombin time was normal. Serum proteins measured 7.1 Gm. per cent, albumin 4.5, and globulin 2.6 Gm. per cent. Stools were negative for bile but contained a trace of urobilinogen. Five stools were negative for occult blood. Repeat liver function studies 1 week after admission revealed a negative cephalin flocculation and a serum bilirubin of 14 mg. per cent. Bile was still present in the urine and absent from the stools. There was no urobilinogen in either the stool or urine specimens.

Course in the Hospital.—It was felt that this patient had a complete obstructive jaundice probably caused by a neoplasm in the head of the pancreas. On May 3, 1948, exploratory laparotomy was carried out. At the time of operation the entire biliary tract was found to be dilated and a hard mass was felt in the head of the pancreas. There was induration in the body and the tail of the pancreas as well. Three biopsies were taken from the mass in the hand of the pancreas and frozen section studies were carried out. In each instance a competent pathologist made a diagnosis of chronic pancreatitis. Accordingly, a simple shunt operation was performed, anastomosing the gall bladder to a loop of jejunum. On the first postoperative day permanent paraffin sections of the third biopsy specimen revealed a nest of carcinoma cells, and thus the diagnosis was changed from chronic pancreatitis to adenocarcinoma of the pancreas. The patient's family was informed of this; re-exploration with an attempt at radical resection of the lesion was refused. Postoperatively the patient's course was uneventful and the elevated serum bilirubin gradually subsided to normal. He was discharged on May 29, 1948.

Follow-up note on this patient following his discharge revealed that he died at home on Feb. 7, 1949, and no autopsy was obtained. Presumably the patient died from carcinoma of the head of the pancreas.

Comment.—This case demonstrates the difficulty in making the diagnosis when a biopsy is taken of a mass in the head of the pancreas. It is well known that when a tumor causes occlusion of the main pancreatic ducts, the resultant obstruction leads to an associated pancreatitis. This inflammatory process may be so extensive that it will completely overshadow the tumor on histologic examination. The positive diagnosis of tumor in this case could be established only after a careful study of the permanent paraffin sections of the tissue obtained from 3 different biopsy sites.

CASE 4.—L. P. (R-26 813), a 53-year-old white man, was admitted to the Albuquerque Veterans Hospital on Aug. 13, 1948 with the chief complaint of abdominal pain and jaundice. This patient first noted occasional nausea and epigastric distress following meals 6 months prior to admission. This pain was relieved by bicarbonate of soda and did not progress until about 1 month prior to admission. At that time he noted severe pain in the epigastrium and right upper quadrant associated with vomiting on 4 occasions. Three weeks prior to admission he noted pruritus, but did not observe any evidence of jaundice until 1 week prior to admission. When jaundice was first noted he also observed that the stools were clay-colored and that the urine became deep in color. There was a weight loss of 15 pounds during the preceding 6 months. There was no history of chills or fever and no disturbance in the bowel habit.

Physical Examination.—The patient was a markedly emaciated white man who was deeply jaundiced. Positive physical findings were limited to the abdomen. There was no evidence of distention nor ascites. The liver edge was palpable 1 fingerbreadth below the costal margin; it was firm, smooth, and nontender. There was some deep tenderness in the right upper quadrant on deep palpation but no masses could be felt. There was no evidence of dilatation of the superficial abdominal veins.

Laboratory Studies.—Hemogram was normal. Urine examination was positive for bile and negative for urobilinogen. Stool examination revealed no bile, a trace of urobilinogen and no blood. Liver function studies showed serum bilirubin 5.8 mg. per cent, icterus index 84 units, prothrombin time normal. Cephalin flocculation test was negative. Thymol turbidity revealed 2 units. Serum proteins were 7.3 Gm. per cent with normal albumin/globulin ratio. Serum amylase was 4 units. Upper gastrointestinal series was negative.

Course in the Hospital.—It was felt that this patient had a complete obstructive jaundice and laparotomy was carried out on Sept. 9, 1948. When the abdominal cavity was opened marked dilatation of the entire biliary tract was noted. The gall bladder contained clear, white bile. There was no evidence of calculi. The common duct was opened and in its distal portion near the superior border of the duodenum it was found to be completely occluded by an extrinsic mass in the head of the pancreas. This mass was very hard and appeared to extend from the head of the gland out into the proximal portion of the body of the pancreas. A biopsy was taken from the area of the head of the pancreas in which the induration seemed to be maximal. Frozen section report of this revealed normal pancreatic tissue. In attempting to take a biopsy from a deeper portion of the head of the pancreas, brisk hemorrhage was encountered deep in the substance of the gland and it was with some difficulty that this hemorrhage was controlled by mattress sutures. The patient's condition, which was not too satisfactory at the start of the procedure, now deteriorated to such a point that it was deemed advisable to place a T tube in the common duct and to close the abdomen as quickly as possible. It was felt at the conclusion of the laparotomy that the lesion was a large carcinoma of the head of the pancreas causing complete biliary tract obstruction. Postoperatively the patient's course was stormy during the first 3 or 4 postoperative days but his vital signs returned to normal on the fourth day. The drainage of clear bile from the T tube was profuse. The icterus index gradually returned to a normal level. Some 28 days after the operation it was found that bile was present in the stool. Simultaneously urobilinogen appeared in the patient's urine for the first time since admission.

On Dec. 6, 1948, the T tube came out unexpectedly during the night and could not be replaced. The sinus tract continued to drain bile for 3 days but then sealed over and no further biliary drainage was noted. At the same time the patient continued to have brown stools and there was no evidence of any collection of bile in the peritoneal cavity on physical examination. He gradually gained weight and was discharged on Feb. 3, 1949, without jaundice, with a healed abdominal wound.

In July, 1949, the patient had a recurrence of jaundice and was re-explored at another hospital. A hard mass was again found in the head of the pancreas. The duodenum was opened and the papilla of Vater was found to be normal. Several lymph nodes were biopsied with no evidence of tumor. A cholecystojejunostomy was done with an operative diagnosis of chronic pancreatitis with resultant stricture of the distal common duct. Postoperative course was uneventful and in October, 1949, the patient was free of jaundice and was gaining weight.

Comment.—Although it was felt at the time of the first operation that this patient had a tumor in the head of the pancreas, the subsequent course tends to cast doubt on this diagnosis. Although no tissue diagnosis is available, it seems unlikely that the obstructive jaundice would subside following simple drainage of the biliary tract if the underlying lesion were carcinoma. Together with this, he has now survived 20 months following the onset of symptoms. This period of survival is additional presumptive evidence that the lesion in the pancreas is benign.

DISCUSSION

In all papers relating to this subject each author touches upon the difficulty of making a tissue diagnosis with certainty at operation when the tumor is in the head of the pancreas. All agree that our present technique for a frozen section study of a nodular mass in the gland has its shortcomings. The organ is difficult to biopsy with safety and chronic pancreatitis is so frequently associated with carcinoma that the malignancy may not be included in the section. The standard method at the present time is to search for distant metastases or suspicious lymph nodes which may give a tissue diagnosis of tumor. However, if positive results are not forthcoming by this maneuver, the majority of surgeons feel that the radical procedure is justified on a gross pathologic diagnosis alone. In 3 of the 4 cases cited above, if this course of action had been followed an unnecessary radical operation would have been performed. Although this experience is an unusual one, it appears that the incidence of benign lesions in this region causing confusion with carcinoma on gross examination is appreciable, ranging from 10 to 19 per cent in the reports of Hartman[13] and Cattell.[2]

Because of this difficulty, several investigators[16, 17, 18] have recently attempted to make a preoperative differential diagnosis by the use of the secretin test. The reported results to date do not appear to indicate that this test has any great value in differentiating between chronic pancreatitis and carcinoma of this organ. The additional examination of the duodenal contents for tumor cells using the Papanicolaou technique has promise, as Whipple[19] has reported 1 case of a carcinoma of the ampulla which was diagnosed preoperatively in this manner. Whether this technique will be profitable when the tumor is in the head of the pancreas, with occlusion of the main pancreatic duct due to the desmoplastic reaction characteristic of these tumors, is problematical.

With the high immediate mortality rate of pancreaticoduodenectomy it does not appear justifiable to carry out the radical resection without histologic confirmation of the presence of carcinoma. On the other hand it may well be stated that those patients with malignant tumors on whom a positive biopsy cannot be obtained will be deprived of the chance for a cure of the lesion. The accumulated experience over the past 14 years has been so uniformly disappointing, as far as the 5 year survival rate is concerned, that some surgeons are beginning to doubt the feasibility of the procedure when the lesion is in the pancreas. Cattell[2] stated in his discussion of tumors in this region that "It must be admitted that no patient with carcinoma of the head of the pancreas has yet been cured or survived five years or more. While many of these patients have a smooth recovery and are quite comfortable for a number of months, the duration of their life following resection hardly justifies such a major procedure since satisfactory palliation might have been procured by a sidetracking operation for the relief of the obstructive jaundice."

In the past the various palliative procedures carried out for the relief of obstructive jaundice have carried a mortality rate ranging from 21 to 63 per cent. Recently Cattell,[2] however, has reported a series of 22 consecutive cases in whom the immediate mortality rate was zero. Although the average length of survival in this group (9.2 months) is shorter than in those patients with carcinoma of the head of the pancreas treated by the radical method (11 months),[2] the difference is not marked. The absence of any mortality in Cattell's palliative procedure speaks strongly in favor of the less radical operation.

When the primary tumor causing obstructive jaundice is in the ampulla or in the periampullary area, the chance of a 5 year survival following radical operation, although small, is definitely present. In reviewing all of the cases up to 1941, Hunt[20] found that about 14 per cent of the patients surviving a resection of the tumor were living and well from 3 to 22 years postoperatively. Recently Cattell[2] reported 3 patients out of 12 who have now survived more than 5 years. In practically all instances a positive tissue diagnosis can be made at the time of laparotomy if a duodenostomy, or rarely a choledochostomy, is performed. With a positive histologic diagnosis at hand the surgeon may proceed with a radical procedure with a clear conscience, and with the knowledge that there is a possibility, however small, that a 5 year survival may be expected.

CONCLUSION

1. Because of the possibility that chronic pancreatitis may be the cause of a mass in the head of the pancreas producing obstructive jaundice, it is felt that radical pancreaticoduodenectomy is not justified without a histologic diagnosis of malignant tumor.

2. If a positive diagnosis cannot be established a palliative sidetracking cholecystoenterostomy should be carried out.

3. Radical surgery for tumors in the ampulla of Vater and in the periampullary region appears to be indicated, for a microscopic diagnosis of malignant tumor is nearly always possible and a small number of 5 year survivors have been reported following this procedure.

SUMMARY

Four case histories are presented in which diagnostic difficulty was experienced at the operating table in determining the nature of a mass in the head of the pancreas producing obstructive jaundice. In 3 of the 4 cases it appears that the cause of the obstruction was not due to carcinoma, but was due to chronic pancreatitis. It is suggested that in the absence of a tissue diagnosis of malignant tumor, a conservative cholecystoenterostomy be done in preference to a pancreaticoduodenectomy.

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CARCINOMA OF THE STOMACH FOLLOWING SURGERY FOR CHRONIC DUODENAL ULCER

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CARCINOMA of the stomach is encountered infrequently as a complication of gastroenterostomy or gastric resection for chronic duodenal ulcer. A comprehensive review of the literature reveals only 27 verified cases. In 20 of these cases the ulcer which necessitated the initial operation was situated in the duodenum, while in the remaining 7 cases the lesion was stated or presumed to be in the pylorus.

The first report of a carcinoma of the stomach developing after gastroenterostomy for pyloric ulcer was published by Schwarz (quoted by Singer) in 1926. His patient, after having undergone an anterior gastroenterostomy for ulcer in 1909, remained well for 6 years. Symptoms of weight loss and vomiting then appeared. At the second operation a gastric neoplasm was found involving the gastroenteric stoma. The regional lymph-nodes and peritoneum were invaded. A palliative Braun anastomosis was performed.

The second case was reported by Beatson,[1] also in 1926. His patient was a 52-year-old conductor who in 1910 underwent a gastroenterostomy for dilatation of the stomach. Since the findings at the original operation were not available, Beatson predicated a pyloric ulcer as the initial lesion, basing his opinion on the clinical history of the case. The patient was explored in 1921 for recurrence of symptoms and a cancer of the lesser curvature involving the enteric stoma was found. The lesion was deemed inoperable.

Hurst and Stewart (quoted by Ransom) published a case in 1929 without presenting any clinical history. Balfour,[2] in1930, in an analysis of 500 consecutive cases of duodenal ulcer treated by gastroenterostomy during the years 1918 and 1919, failed to find a single instance of carcinoma developing during a 10 year period subsequent to surgery.

Singer,[3] in 1932, reported a carcinoma of the stomach developing in a 52-year-old man who in 1918 underwent a pylorectomy, posterior gastroenterostomy, and cholecystectomy for a duodenal ulcer and cholecystitis. Eleven years later the patient was readmitted for investigation of symptoms consisting of postprandial pain, bloating, and eructation. No lesion was found by x-ray examination. In 1930 laparotomy was done for recurrence of severe and frequent episodes of postprandial pain. A polypoid carcinoma was found in the region of the anastomosis. The gastroenterostomy was disconnected and the segment of the stomach containing the tumor resected. A Billroth II type of anastomosis was performed. The patient died of postoperative hemorrhage on the second day.

Wilbur and Rivers,[4] in 1932, analyzed 33 cases of proved duodenal ulcer associated with gastric carcinoma from the records of the Mayo Clinic. Four of these had undergone gastroenterostomy previously and a fifth had had an excision of the ulcer and a pyloroplasty. In 1935, Lurje[5] added a case in which the initial lesion was a pyloric ulcer. The following year Ransom[6] reported the case of a 42-year-old man who in 1927 had had a gastroenterostomy for a duodenal ulcer. Seven years later at exploration for abdominal pain, vomiting, diarrhea, weakness, and loss of weight, a scirrhous carcinoma was found involving the distal one-half of the stomach and the adjacent segment of jejunum. In 1936, Bertini[7] surveyed the world literature and reported a case of his own following surgery for a pyloric ulcer. Six years later Kneringer[8] described a gastric carcinoma developing 18 years after a gastric resection, Billroth II, for a duodenal ulcer. In 1944, Rodriguez and D'Alotto[9] published their report of a patient who was found to have a gastric neoplasm 10 years after gastroenterostomy for a duodenal ulcer. Two years later Montanari[10] added 2 more cases. The first was a 41-year-old patient who at operation 4 months after a gastroenterostomy for duodenal ulcer was found to have a carcinoma of the stomach adjacent to the enteric stoma.

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The second was a 37-year-old patient who developed a gastric neoplasm 4 years after a resection and Polya repair for a duodenal ulcer.

The single largest group of cases was reported from the Mayo Clinic in 1948 by Gray and Lofgren.[11] Of 825 consecutive cases admitted between Jan. 1, 1938, through Dec. 31, 1947, in which a gastroenterostomy had previously been performed for duodenal or gastric ulcer, 11 gastric carcinomas developed after surgery for duodenal ulcer (Table I).

TABLE I. CHRONOLOGICAL DATA ON CARCINOMA OF THE STOMACH FOLLOWING SURGERY FOR DUODENAL ULCER

DATE	AUTHOR	NUMBER OF CASES	SITE OF ULCER	INITIAL OPERATION
1926	Schwarz	1	Pylorus	Gastroenterostomy
1926	Beatson	1	Pylorus (?)	Gastroenterostomy
1929	Hurst and Stewart	1	Duodenum	Gastroenterostomy
1932	Singer	1	Duodenum	Pylorectomy and gastroenterostomy
1932	Wilbur and Rivers	5	Duodenum	Gastroenterostomy (4); excision of ulcer and pyloroplasty (1)
1935	Lurje	1	Pylorus	Gastroenterostomy
1936	Ransom	1	Duodenum	Gastroenterostomy
1936	Bertini	1	Pylorus	Gastroenterostomy
1942	Kneringer	1	Duodenum	Gastric resection
1944	Rodriguez and D'Alotto	1	Duodenum	Gastroenterostomy
1946	Montanari	2	Duodenum	Gastroenterostomy; gastric resection
1948	Gray and Lofgren	11	Duodenum	Gastroenterostomy
	Total	27		

From the records of the Mount Sinai Hospital, New York, reviewed from 1933 to 1949, 1,160 patients were found in whom a diagnosis of carcinoma of the stomach was made. The diagnosis was confirmed in 944 of these cases by either operation or post-mortem examination. Only 5 patients presented a history of a previous gastroenterostomy or gastric resection for duodenal or pyloric ulcer.

The patients, 4 of whom were men, ranged in age from 48 years to 73 years (Table II). The ulcers which necessitated the initial operations were stated to be duodenal in 3 patients, at the pylorus in 1, while in the remaining case it was not indicated, the presumption being that it was located in the duodenum. The initial operation was a subtotal gastrectomy in A. S. (Case 1) and gastroenterostomy in the remaining 4 patients. The symptom-free interval after the first operation varied from 5 years to 40 years. J. B. (Case 2) had 3 episodes of melena occurring at 5 year intervals between the initial and last operation. W. W. (Case 5) was admitted 12 years after gastroenterostomy for symptoms said to be due to a peptic ulcer. He responded to conservative therapy and remained free of symptoms for the next 12 years.

Duration of symptoms before the last operation varied from 5 weeks to 10 months. In all of the patients, melena or weight loss was noted. In only 3 was a history of pain elicited.. In 2 of the patients with symptoms of shorter duration, 2 months and 5 weeks, respectively, pathologic examination of the resected specimens failed to reveal lymph node involvement. In the 3 cases in which gastric resection was possible, the carcinoma was found to have involved the gastroenteric anastomosis.

TABLE

PATIENT	AGE	SEX	SITE OF ULCER	INITIAL OPERATION	SYMPTOM-FREE INTERVAL (YEARS)	DURATION PRESENT ILLNESS	SYMPTOMS
Case 1, A. S. (No. 505400)	53	M	Duodenum	Subtotal gastrectomy, 1932	11	10 months	Pain, hematemesis, melena, weight loss
Case 2, J. B. (No. 587793)	48	M	Duodenum	Gastroenterostomy, 1933	5*	2 months	Melena
Case 3, J. S. (No. 590270)	60	F	Duodenum ?	Gastroenterostomy, 1908	40	6 months	Pain, melena, weight loss
Case 4, L. M. (No. 510765)	61	M	Duodenum	Gastroenterostomy, 1926	17	5 weeks	Pain, anorexia, weight loss, vomiting
Case 5, W. W. (No. 601088)	73	M	Pylorus	Gastroenterostomy, 1925	12†	6 weeks	Anorexia, weight loss, melena, weakness

*Recurrent episodes of melena, 1938, 1943, and 1948.
†Admitted with ulcer symptoms, 1937.

L. M. (Case 4) and W. W. (Case 5) were operative mortalities. A. S. (Case 1) died of carcinoma following discharge from the hospital. The 2 remaining patients, J. B. (Case 2) and J. S. (Case 3), are still alive.

DISCUSSION

The infrequency with which carcinoma of the stomach is encountered after operative intervention for duodenal ulcer is affirmed by the paucity of reports of this lesion in the literature. To the 27 cases that have been found, 5 additional cases have been collected from the records of the Mount Sinai Hospital out of 1,160 cases diagnosed as carcinoma of the stomach, representing an incidence of 0.4 per cent.

The recurrence of severe, intractable epigastric pain, melena, hematemesis, anorexia, and weight loss following surgery for duodenal ulcer generally indicates the development of a benign marginal ulcer. However, in a small number of patients in whom these symptoms appear the underlying lesion is not a benign gastrojejunal ulcer at the anastomosis but rather a carcinoma of the stomach. It is in these patients that an early and accurate diagnosis must be made in order to institute prompt surgical therapy. Neither the history of a preceding duodenal ulcer nor the presence of significant concentrations of free hydrochloric acid in gastric aspirations (J.B., Case 2) excludes a possible diagnosis of carcinoma. Evaluation of the clinical picture with the assistance of gastroscopy and roentgen studies of the gastrointestinal tract aids in establishing the true character of the lesion.

SUMMARY

1. A comprehensive review is made of the existing literature on carcinoma of the stomach following gastroenterostomy or gastric resection for chronic duodenal ulcer.

II

GASTRIC ANALYSIS FREE HCl	GASTRO-INTESTINAL SERIES	OPERATIVE FINDINGS	OPERATIVE PROCEDURE	PATHOLOGY	POST-OPERATIVE COURSE
Achlorhydria	Lesser curvature mass	Inoperable carcinoma of stomach	Exploratory laparotomy, 1943		Uneventful
60 meq.	Old and active duodenal ulcers	Carcinoma of stomach invading anastomosis	Subtotal gastrectomy, jejunectomy, 1948	Mucous-cell carcinoma; no lymph node involvement	Uneventful
Achlorhydria		Carcinoma of stomach invading anastomosis	Subtotal gastrectomy, jejunectomy, 1949	Polypoid carcinoma; lymph nodes involved	Uneventful
	Gastric mass distal to anastomosis	Carcinoma of stomach invading anastomosis	Subtotal gastrectomy, 1943	Carcinoma simplex; no lymph node involvement	Died 25th P.O. day
17 meq.		Carcinoma of mid-stomach; metastases to pre-aortic nodes	Exploratory laparotomy, 1949		Died 3rd P.O. day

2. Details of 5 additional cases are presented.

3. An incidence of 0.4 per cent of cases with a preceding history of surgery for duodenal ulcer is noted out of 1,160 cases of diagnosed gastric carcinoma from the Mount Sinai Hospital during the years 1933 to 1949.

4. Attention is directed to the fact that the recurrence of severe intractable epigastric pain, melena, hematemesis, anorexia, and weight loss following surgery for duodenal ulcer may indicate the development of a carcinoma of the stomach.

Acknowledgment.—I am indebted to Dr. John H. Garlock for permission to report Case 4.

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OBSERVATIONS ON CHRONIC OBSTRUCTION OF THE ABDOMINAL AORTA

LERICHE'S SYNDROME

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CHRONIC obstruction of the abdominal aorta has not been considered as an important factor in the circulatory disturbances of the lower extremities in spite of its being of more frequent occurence than has been expected. The absence of serious ischemic symptoms accompanying a complete obstruction of the aorta was misleading until Leriche, in 1940, separated it as a clinical entity and described the symptoms on which the diagnosis and treatment are based. After the publication by Leriche, Martorell,[10, 11, 12, 13] Moulonguet,[16] Morel,[14, 15] Delannoy,[3] Ameline,[1] Servelle,[19] Christophe,[2] Paul,[17] Price,[18] Leriche,[8] and lately Elkin,[5] have reported cases of complete obstruction, but none of them have mentioned the incomplete obstructive type.

It is rather difficult to establish, basing conclusions on only post-mortem statistics, the frequency with which the disease occurs. Siegel and Garvin[20] found 9 cases among 6,457 autopsies. Lueth[9] published similar figures, and according to these authors the frequency would be 0.12 per cent. We think these figures are rather low taking into consideration the fact that we have observed 13 cases in the last 2 years.

Primary obstruction of the aorta is rare because seldom is an isolated arteriosclerotic or inflammatory lesion capable of determining thrombosis of this organ. Usually, the bilateral obliteration of the iliac arteries secondary to atheromatous changes is the factor responsible for the aortic thrombosis. Obliteration of one of the iliac arteries alone gives way to a unilateral ischemic syndrome but in such a case we have not observed thrombosis of the aorta.

Along with this factor, which, by the way, is the most frequent, thrombosis of the aorta may develop following the recovery from an embolus. Morel reported 1 case secondary to thromboangiitis obliterans of both iliac arteries. Other factors that have also been considered are: syphilis, various arteritis, peritoneal inflammatory processes, and deep x-ray therapy on the abdomen.

In 4 of our observations, in which anatomic studies of the aorta were made, we found obliterating arteriosclerotic lesions of both iliac arteries and secondary thrombosis of the aorta.

The aorta thus obstructed acts as a reflex center capable of producing distant spasm that would explain the clinical symptoms which are observed in these cases, which is one of the reasons why Leriche has advocated aorto-iliac resection as the proper method of treatment, but only in cases of complete obstruction. If it is done in the incomplete obstructive type the abrupt vascular occlusion thus created may originate an acute ischemic syndrome.

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Symptomatology.—The disease generally commences insidiously and the patients will complain of coldness and easy fatigability along with weakness of the lower limbs on walking. In a more advanced period the symptomatology will depend upon the condition of collateral circulation; bilateral intermittent claudication will appear together with loss of sustained erection, which is a valuable sign in young patients.

Aortic obstruction is at first compensated for a long period of time, usually 5 to 10 years, before trophic symptoms appear, but, invariably, after distant extension of the thrombosis, peripheral gangrene develops. In other instances the progression of the thrombosis is proximal and the occlusion of the mesenteric and renal arteries will produce such serious visceral complications that death may result, as occurred in 2 of our cases.

The physical findings may be sufficiently demonstrative to make the diagnosis possible. They are: (1) Absence of pulsation and oscillation in both inferior extremities, (2) absence or greatly diminished pulsation in both iliac arteries and infra-umbilical segment of the aorta, (3) muscular atrophy with loss of the hair of the lower limbs, which at the same time may present a more or less marked discoloration. In the terminal stages, serious ulcerative or gangrenous bilateral lesions may be observed, which should make one suspect an aortic obstruction; but in some cases the lesion may be unilateral and very difficult to differentiate from those following obstructions of other peripheral arteries.

X-ray Exploration.—Although the clinical symptoms and physical signs are nearly always sufficient to make a diagnosis of aortic obstruction, its extension and site will be unknown if an x-ray examination of the abdominal aorta with the aid of an opaque substance is omitted. We do this exploration systematically and have been surprised to observe in 2 cases an incomplete obstruction when the clinical picture suggested a complete type.

Aortography gives interesting information concerning the collateral circulation which is of great importance to establish the indications and contraindications for surgical treatment. In our first 4 cases the retrograde technique was employed; the femoral artery was selected for the injection of the contrast medium. In all the rest, the direct puncture of the abdominal aorta through the back, as recommended by Dos Santos,[4] was employed. We prefer this latter method because it gives exact information of the type of obstruction and of its precise localization, and at the same time is an easy technique and devoid of complications.

Surgical Treatment.—The ideal form of treatment would be to resect the thrombosed area and bridge the gap with a vessel graft, but this is impossible in such cases. In selected cases the collateral circulation is improved by bilateral resection of the lumbar sympathetic chains and a resection is made of the terminal portion of the aorta and both iliac arteries as proposed by Leriche. By doing this, the area of irritation which will cause distant spasm of vessels still patent is suppressed and at the same time the thrombotic area, which otherwise would continue to extend with fatal results, is removed.

Resection is, of course, contraindicated when the thrombosis ascends centrally, reaching the vicinity of the renal arteries, because in marked sclerotic aortas it would be very difficult to ligate or suture the severed vessel without interfering with the circulation in those important vessels. Some of these aortas are very difficult to treat once severed. Sometimes they are intensely adherent to surrounding tissues. In some of these cases we have used umbilical tape to tie them successfully. We have always done resections of the bifurcation of the aorta preceded by a one-sided sympathectomy, and, 1 week or more later, the

Fig. 1 (Case 1).—Retrograde aortography showing incomplete obstruction of abdominal aorta, and efficient collateral circulation. Renal stones are visible.

resection along with sympathectomy of the other side. In some cases we have performed the operation extraperitoneally and in others transperitoneally, which we think is easier, giving a better exposure. From our short number of cases we cannot draw any definite conclusions of what we may call Leriche's operation, although in 2 of our cases we obtained promising results.

CASE REPORTS

Case 1.—P. S. C., a white man, 55 years of age, came to the service on Nov. 4, 1947, complaining of bilateral intermittent claudication and loss of sustained erection for the past 7 years.

Examination disclosed mild muscular atrophy of the lower limbs, coldness, a moderate cyanotic discoloration, and absence of pulsation and oscillations. Blood pressure was 180/100. Aortography by retrograde technique showed an incomplete aorto-iliac obstruction with a rich collateral circulation. Numerous stones were present in the kidneys.

The general condition of the patient was so bad that no surgical measures were advised. Six months later, the patient died at home. No post-mortem could be obtained.

CASE 2.—P. G. L., a white man 61 years of age, entered the hospital on March 13, 1948, complaining of bilateral intermittent claudication and difficulty in erection of 10 years' duration. He complained also of continuous pain in the left foot during the past 3 months.

Examination revealed cyanotic discoloration of the toes and inner border of the left foot with a plaque of gangrene under the nails, marked muscular atrophy of the lower limbs, and absence of arterial pulsations and oscillations. Blood pressure was 180/100. Retrograde aortography showed complete obstruction of the abdominal aorta and rich collateral circulation.

Fig. 2 (Case 2).—Retrograde aortography showing complete obstruction of abdominal aorta and efficient collateral circulation.

Bilateral lumbar sympathectomy was performed with some improvement of the trophic lesions and lessening of pain. The intermittent claudication was not influenced favorably. Resection of the aorta was abandoned because of the marked arteriosclerotic lesions of its wall and the firm adhesions to the surrounding tissues. We have not seen this patient recently.

CASE 3.—L. R., a white man 58 years of age, came to the hospital May 24, 1948, complaining of intermittent claudication and night cramps of the lower limbs which had started 3 years previously and had progressed to the point of invaliding him.

Examination disclosed marked atrophy of the lower limbs along with absence of oscillations and pulsations of the arteries. Blood pressure was 175/100. Retrograde aortography showed complete obstruction of the abdominal aorta with a poor collateral circulation.

Fig. 3 (Case 4).—Retrograde aortography, showing complete obstruction of abdominal aorta and efficient collateral circulation.

Fig. 4 (Case 4).—Microscopic appearance of one of the iliac arteries.

Fig. 5 (Case 8).—Posterior arteriography (by direct puncture), showing obstruction of the aorta, and collateral circulation of the mesomesenteric type.

Fig. 6 (Case 8).—Aorta and iliac arteries.

Sympathectomy was advised, but was not accepted by the patient. We followed him for 6 months, in which time his symptoms progressed. He has not reported again.

CASE 4.—E. R., a white man 44 years of age, was admitted to the hospital on July 7, 1948, complaining of sexual impotence and sharp pains in both legs of 2½ years' duration. During the last 6 months walking had been impossible.

Examination disclosed a very painful ulcer on the anterior aspect of the right leg which had not improved under intense local treatment during the 6 months previous to admission. Muscular atrophy of the lower limbs was very marked. Neither oscillations could be seen nor arterial pulsations could be felt. Both legs, when elevated, turned intensely pale. Aortography demonstrated a complete obstruction of the abdominal aorta with efficient collateral circulation.

A right lumbar sympathectomy was carried out and 20 days later a left lumbar sympathectomy was done along with aorto-iliac resection. Postoperative course was good. Pain disappeared immediately after the operation but the ulceration persisted for some time. This patient was free of pain and walking freely 1 year after the operation. He also regained sexual potency.

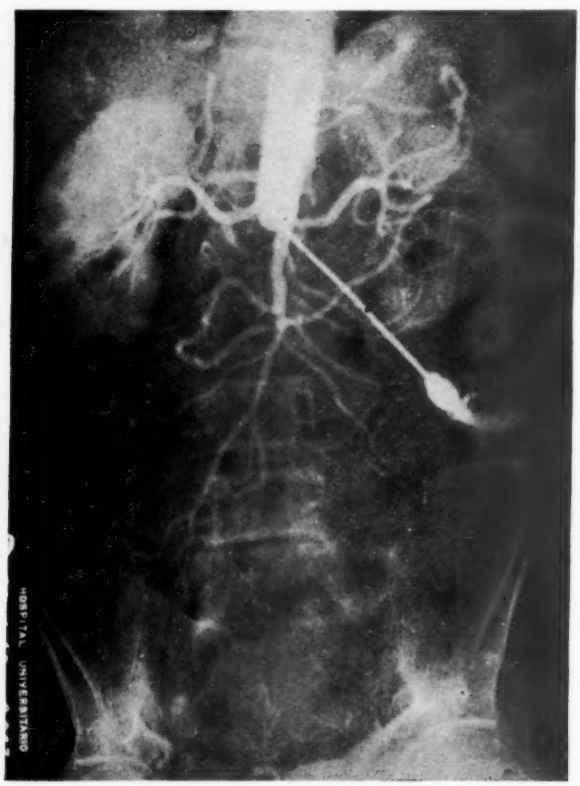

Fig. 7 (Case 5).—Posterior aortography, showing obstruction of abdominal aorta. Renal arteries and superior mesenteric with its branches are clearly shown.

CASE 5.—P. C. P., a white man 60 years of age, came to the hospital on Nov. 9, 1948. He complained of bilateral intermittent claudication, night cramps of the legs, and loss of sustained erection for the previous 6 years. During the past 12 months he had not been able to walk more than 20 yards.

Exploration revealed absence of pulsations and oscillations of the lower limbs which were cold and showed marked muscular atrophy but no trophic signs. Blood pressure was 130/70. Posterior aortography showed a complete obstruction of the abdominal aorta below the renal arteries.

Operation was advised but not accepted by the patient. Treatment was instituted with antispasmodics and anticoagulants for 1 month without any improvement. Eleven months later he was seen again; he was much worse, and complained of sharp pains even at rest and claudication as soon as he started to walk.

CASE 6.—A. H. C., a mulatto man 57 years of age, came to the hospital Nov. 27, 1948, complaining of intermittent claudication of both lower limbs of 4½ years' duration. During the previous months he began to complain also of night cramps of the legs.

Examination showed no arterial pulsations nor oscillations in the lower limbs. The extremities were pale and cold but without any trophic signs. Blood pressure was 190/130. After posterior aortography a complete obstruction of the abdominal aorta was evident. Both renal arteries and the superior mesenteric were clearly visualized in the plate.

Bilateral lumbar sympathectomy in 2 stages was performed and the patient was relieved of the intermittent claudication, but died 4 months later of mesenteric thrombosis. This case demonstrates the possibility of proximal extension of the thrombosis without accompanying trophic symptoms.

Fig. 8 (Case 7).—Posterior aortography (by direct puncture), showing incomplete obstruction of abdominal aorta. The outline of the vessel is irregular as is its terminal narrowing. Iliac arteries, especially the left, are poorly shown.

CASE 7.—F. D., a Negro woman 48 years of age, was admitted on Feb. 3, 1949, on account of a painful ulcer of the right leg which she had had for the past 2 years. It had not healed, in spite of local treatment. She stated also that for the past 4 years her legs principally the right one, felt tired after walking 200 or 300 yards.

Examination disclosed all the signs pointing to a complete obstruction of the abdominal aorta, but at the same time a thrill was noted in both inguinal regions. Blood pressure was 180/100. Posterior aortography demonstrated an incomplete aortic obstruction along with very thin and poorly visualized iliac arteries.

Right lumbar sympathectomy was done and 2 weeks later the left lumbar trunk was also removed. During the operation the aorta was palpated and a feeble pulsation was noticed. Postoperative course was uneventful and the ulcer healed in 3 weeks, but claudication persisted 4 months later. Without an aortography this case would have been diagnosed clinically as an incomplete obstruction.

Fig. 9 (Case 11).—Posterior aortography (by direct puncture), showing obstruction of abdominal aorta. Hepatic and splenic arteries are clearly shown; renal arteries are poorly shown.

CASE 8.—A. N. M., a white man 49 years of age, entered the hospital on March 3, 1949, complaining of intense pain of the lower limbs in spite of being at rest for several months. He had been suffering intermittent bilateral claudication and sexual impotence for 15 years but his actual pains began 1 year ago and during the past 2 months he could not walk and had to be in bed.

Both inferior extremities were cold and showed a marked muscular atrophy. Arterial pulsations could not be felt and oscillations were not seen. No trophic symptoms were evident. Posterior aortography showed a complete obstruction of the abdominal aorta with a very good visualization of the circulation of both mesenteric arteries.

A right lumbar sympathectomy was done, and 15 days later a left lumbar sympathectomy was performed, along with the resection of both iliac arteries and the abdominal aorta just distal to the emergence of the inferior mesenteric artery. Pain disappeared immediately and notable increase of local temperature of both limbs was also observed. He left the hospital

walking without any claudication. Seven months later he was still free of pain, but had mild symptoms of claudication after walking more than 200 yards. He still has not regained sustained erection.

CASE 9.—L. A. P., a white man 52 years of age, came to the hospital on March 15, 1949, complaining of acute pains even at rest in both lower extremities. It was impossible for him to walk. He complained of bilateral intermittent claudication, more pronounced on the right side, for the past 10 years. Three months ago he had an ulcer on the right foot which took 2 months to heal. Since the present illness began he complained of loss of sustained erection, becoming completely impotent for the last 6 years.

Fig. 10 (Case 11).—Terminal aorta with iliac arteries.

Examination disclosed extreme coldness of both lower limbs, with marked muscular atrophy and loss of the hair. No pulsation or oscillation could be perceived. There was marked postural ischemia. Posterior aortography confirmed a complete aortic obstruction.

On March 20 a right lumbar sympathectomy was done; it did not alter the cutaneous temperature gradient nor did it relieve the pain. In spite of his very deteriorated general condition and on account of the terrible pain, an aorto-iliac resection seemed necessary. It was done but he died of shock 2 hours later. Post-mortem revealed that the ligatures on the vessels had not given way. Both iliac arteries and also the aorta distal to the renal arteries had arteriosclerotic obliterating lesions.

CASE 10.—M. R., a Negro man 62 years of age, came to the outpatient department on May 3, 1949, complaining of intermittent claudication of the lower extremities during the past

9 years. The symptoms were more marked on the left limb. The claudication had become much worse recently and he could not walk more than 50 yards without having to stop because of sharp pains. He has lately been having pains and night cramps although at rest. During winter the symptoms are generally more pronounced. He had been sexually impotent for the last 10 years. Blood pressure was 260/120.

Clinically it was evident that he was suffering from a complete aortic obstruction. This was confirmed by posterior aortography which showed at the same time a good mesenteric circulation. The intercostal arteries were filled by reflux. Renal circulation was poor although he had a moderate hypertension.

A right lumbar sympathectomy was performed with some subjective improvement; he did not accept a left lumbar sympathectomy. Five months later his condition had not changed.

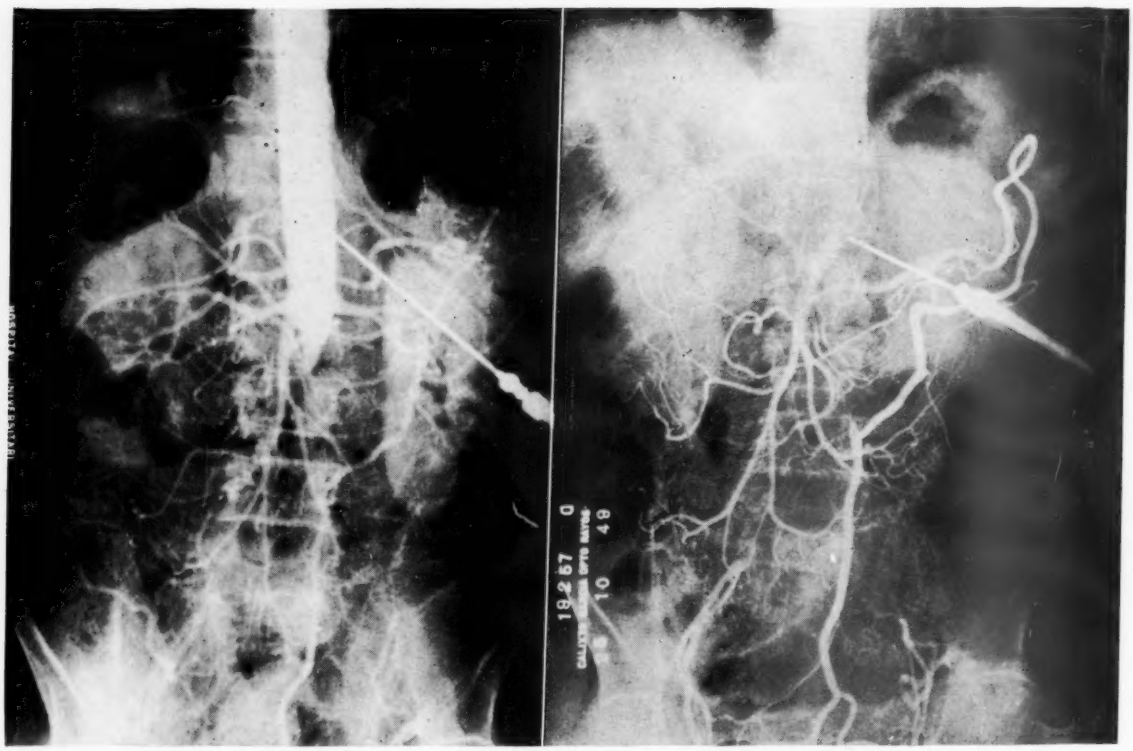

Fig. 11. Fig. 12.

Fig. 11 (Case 12).—Posterior aortography (by direct puncture), showing obstruction of the abdominal aorta, mesomesenteric type of collateral circulation. There is clear visualization of hepatic, splenic, and renal arteries. Intercostal arteries are filled by reflux.

Fig. 12 (Case 12).—Posterior aortography; by selective puncture at the level of the superior mesenteric artery the mesomesenteric type of collateral circulation is clearly shown.

CASE 11.—L. O., a white man 69 years of age, came to us June 3, 1949, with a very painful ulcer of the right foot. For the previous 8 years he had been complaining of intermittent bilateral claudication and night cramps of the lower limbs. An ulcer appeared 1½ months ago and has had no tendency to heal. Even at rest he complained of excruciating pains in the lower limbs.

On examination the lower extremities were moderately cyanotic and presented a marked muscular atrophy. No oscillations nor pulsations could be demonstrated. Blood pressure was 140/90. Posterior aortography showed complete obstruction of the abdominal aorta. The splenic and hepatic arteries were clearly visualized in contrast with the poor visualization of the renal and mesenteric arteries.

Bilateral lumbar sympathectomy was done in 2 stages along with aortoiliac resection in the second stage. The pain improved for 4 weeks after the operation but later on the ulcer progressed, became gangrenous, and a mid-thigh amputation was done. The stump healed per primam.

CASE 12.—F. C. F., a white man 59 years of age, entered the hospital Oct. 22, 1949, with a patch of gangrene on the left foot, with continuous pain for the previous 6 weeks. He had been suffering from easy fatigability of the legs for more than 8 years and for the last 3 years had had frank intermittent claudication, which did not allow him to walk over 100 yards. Since his illness began he had not been able to have sustained erection.

No pulsations or oscillations were present in the limbs, which were also markedly pale and cold. Muscular atrophy was evident. Blood pressure was 150/100. When aortography was done the opaque substance filled the mesenteric arteries but the aorta was not visualized. Some days later a second aortogram was tried; it demonstrated complete obstruction of the aorta and showed again the circulation in the mesenteric arteries. This case is still under observation.

Fig. 13 (Case 13).—Posterior aortography, showing obstruction of the abdominal aorta. Meso-mesenteric type of collateral circulation. Hepatic, splenic, and renal arteries are well filled.

CASE 13.—M. G., a 69-year-old white woman, was admitted on Nov. 15, 1949, for bilateral intermittent claudication of 2½ years' duration which had progressed to the extent of now appearing after she had walked 15 or 20 yards. She complained of easy fatigability of the legs for the past 5 years.

On examination, pulse and oscillations could not be perceived in the lower limbs. No trophic signs were observed and she only had mild muscular atrophy. Blood pressure was

170/100. A plain x-ray plate showed calcification of the iliac arteries and a posterior aortography confirmed a complete obstruction of the abdominal aorta from below the renal arteries.

She is still under observation, her case being our first complete aortic obstruction diagnosed in a woman.

Comments.—We have presented 13 cases of chronic obstruction of the abdominal aorta which demonstrate the relative frequency and great importance the aortic pathology has in the etiology of peripheral vascular disturbances. The symptomatology of these 13 cases was similar to that described by Leriche in his original paper. Bilateral intermittent claudication and disturbance of erection were the predominant subjective symptoms, which, associated with the absence of arterial pulsations and oscillations, permitted a diagnosis of aortic obstruction. In Table I the most outstanding characteristics of the cases are summarized. It is important to point out that the age of the patients varied between 49 and 69 years. Only 2 in our series were women. In 8 of our observations there was an elevated blood pressure in the arms. This fact makes us think that the abdominal aortic obstruction may be the cause of this hypertension.

TABLE I.

CASE	AGE (YEARS)	RACE	SEX	EVOLUTION (YEARS)	BLOOD PRESSURE	TREATMENT	RESULTS
1	55	W	M	7	180/100	Medical	Unknown
2	61	W	M	10	180/100	Medical	Unknown
3	56	N	M	3	175/100	Sympathectomy	Unknown
4	44	W	M	2½	120/ 80	Aorto-iliac resection and sympathectomy	Good
5	60	W	M	6	130/ 70	Medical	Fair
6	57	N	M	4½	190/130	Sympathectomy	No improvement
7	48	N	F	4	170/100	Sympathectomy	Fair
8	49	W	M	15	115/ 60	Aorto-iliac resection and sympathectomy	Good
9	52	W	M	10	180/100	Aorto-iliac resection and sympathectomy	No improvement
10	62	N	M	9	260/120	Sympathectomy	Fair
11	69	W	M	8	140/ 90	Aorto-iliac resection and sympathectomy	No improvement
12	59	W	M	8	150/100	Sympathectomy	Still in study
13	69	W	F	2½	170/100	Medical	Still in study

We wish to emphasize the importance of the radiologic exploration of the abdominal aorta with the aid of an opaque substance because it not only permits one to make the diagnosis but at the same time gives exact information concerning extension of the obstruction and the condition of collateral circulation. In 2 of our cases clinically diagnosed as complete obstruction, aortography showed that the aorta was still patent. Probably these incomplete obstructions would become complete in the future.

In the 4 cases in which the pathology of the aorta could be studied, obliterating arteriosclerotic lesions of the iliac arteries were evident, with

secondary thrombosis of the aorta, as has been pointed out by Martorell. It seems that aortic obstruction only develops following bilateral iliac obstruction for we have always seen aorta patent when one of the iliacs alone was obstructed.

The long evolution these patients undergo and their tardiness in coming to us makes it difficult to select the proper treatment but from the study of our short series we are convinced that medical measures are useless and do not improve any of the symptoms. Lumbar sympathectomy has in some cases improved intermittent claudication and alleviated pain but does not prevent proximal or distal extension of the thrombosis; this was the reason why Leriche recommended resection of the thrombosed segment. In 2 of our 4 patients operated upon satisfactory results were obtained while in the other 2 the operation was a failure.

It is impossible, with such a small series, to draw conclusions respecting the utility of resecting the thrombosed segment, although we think it should be done unless age and anatomic conditions of the aorta make the operation too dangerous.

SUMMARY

1. Thirteen cases of chronic obstruction of the abdominal aorta are presented and its importance in peripheral vascular disturbances is pointed out.

2. Posterior aortography is the method of choice to confirm the diagnosis and study the collateral circulation.

3. Medical treatment was useless in our cases.

4. Bilateral lumbar sympathectomy, associated in 4 cases with aorto-iliac resection, resulted in at least temporal improvement in most of them.

5. In 2 cases the aortic obstruction was incomplete and the importance of the diagnosis from the point of view of treatment is emphasized.

Acknowledgment.—We wish to acknowledge our indebtedness to Dr. Carlos Cardenas, Professor of Medicine, University of Havana, for enabling us to avail ourselves of the facilities of his department in the study of these cases.

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THE CLINICAL PHYSIOLOGY OF THE HUMAN BRONCHI

I. Pain of Tracheobronchial Origin

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THE existence as well as the referral of pain arising from stimulation of the human tracheobronchial tree has not, up to this time, been established. A survey of the early as well as the current literature relating to the anatomy and physiology of the lung and respiratory tree revealed but scanty discussion of the problem, and consequently stimulated this review together with the subsequent clinical studies here presented.

The presence of afferent nerve endings in the tracheobronchial tree of animals has been demonstrated physiologically in a series of experimental procedures carried out by Brodie and Russell,[1] Roger,[2] Mayer, Magne, and Plantefol,[3] Craigie,[4] and Larsell and Burget.[5] This group of investigators stimulated the respiratory mucosa with irritant vapors inhaled through a tracheal cannula, and also with a brush introduced during bronchoscopy. These procedures resulted in a variable respiratory reflex. The studies were performed on animals under general anesthesia, thus precluding any evaluation of the pain or discomfort which might have been produced.

In 1921 Larsell[6] presented histologic evidence of three types of afferent nerve endings in the lung of the rabbit. Correlating the differences in histologic structure of the nerve endings with their anatomic position, he suggested three functional types of sensory termination: (a) bulbous nodules in the trachea and larger bronchi responding to tactile stimulation, (b) thickened epithelial nodules in the bronchioles responding to tactile and collapse stimulation, and (c) thinly encapsulated terminals in the atria, responding to stretch and possibly to chemical stimulation. Studies on man,[7] which were performed later, revealed no fundamental differences.

In 1911, Capps,[8, 9] after stimulating the surface of the lung with a needle introduced through a thoracentesis trocar, concluded that the visceral pleura as well as the pulmonary parenchyma were insensitive to pain. Irritation of the parietal pleura, however, may give rise to pain which is noted in the thoracic wall. Localization of this pain corresponds to the distribution of the intercostal nerve supplying that segment of pleura. Irritation of the central part of the diaphragmatic pleura gives rise to referred pain in the neck, the site of the origin of the phrenic nerve. Irritation of the costal part of the diaphragm gives rise to pain not only in the lower thorax but also in the abdomen and lumbar regions, corresponding to the distribution of the lower six intercostal

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nerves which supply branches to the peripheral part of the diaphragm. Capps' conclusions appear to have established the current viewpoint concerning pain arising from the chest for the majority of authorities on thoracic disease.[10, 11, 12] With but few exceptions no discussion of pain of tracheobronchial origin has been presented. It should be stated, however, that authorities have assumed the possibility of tracheobronchial pain resultant to such a specific entity as acute bronchitis, the symptomatology of which is usually considered to present substernal oppression, a sense of tightness, or pain.

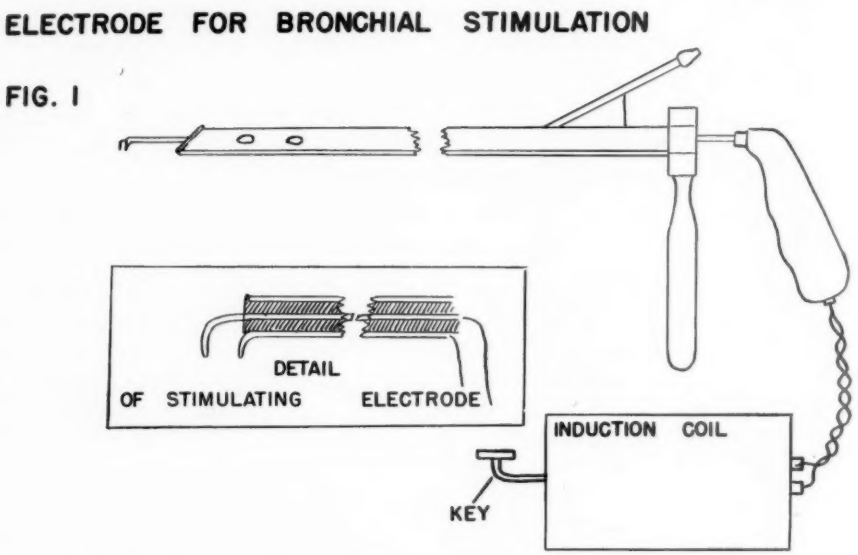

Fig. 1.—Details of the initially constructed stimulating electrode, which proved unsatisfactory in that bronchial secretions often short-circuited the closely apposed points.

White and Smithwick[13] stated that there is no referred pain from the lung, the parenchyma being insensitive; however, they made the assertion that pain arising from the larger bronchi is transmitted over somatic vagal afferent axones. Chevalier Jackson[14] stated that pain appears to be felt more in the bronchi than in the trachea; moreover, he reported that pain is rarely noted during bronchoscopy and is extremely rare when a foreign body lodges in the tracheobronchial tree. On the other hand, Drinker[15] indicated that the trachea and larger bronchi are highly sensitive.

From the foregoing review it appeared that the existence as well as the quality of pain of human tracheobronchial origin had not been well established. Consequently, in an attempt to evaluate the presence or absence, as well as the type and referral of painful sensations arising within the tracheobronchial tree, the following experimental study was accomplished.

CLINICAL INVESTIGATION

These investigations were made upon patients undergoing bronchoscopy. In addition to the usual bronchoscopic instruments, a long, insulated electrode and a 4.5 volt dry cell battery producing an induced current were employed.

Two types of electrodes were designed. The first (Fig. 1) proved to be unreliable since the bronchial secretions often short-circuited the closely apposed points. The second type, however, proved highly satisfactory and is presented in Fig. 2.

The patients were carefully screened to exclude the apprehensive and uncooperative groups. Prior to bronchoscopy they were instructed that a test of the bronchial nerves would be made, and if pain or any unusual sensations were noted to indicate by finger-touching the area where these were felt. The induced current was adjusted by means of a rheostat to the strength necessary to produce discomfort when the electrode was applied to the examiner's tongue.

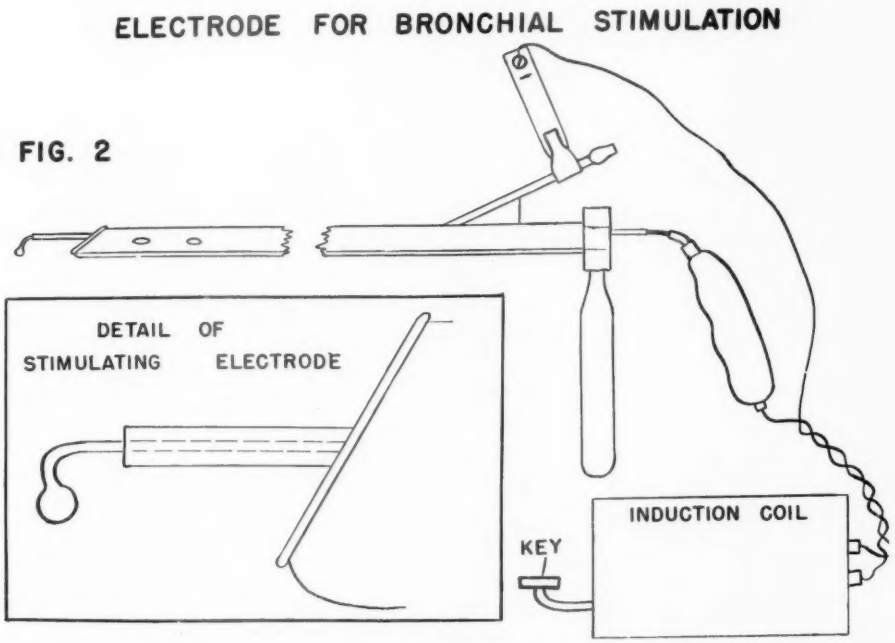

Fig. 2.—Details of the single, spherical, solid-tipped electrode, utilizing the bronchoscope as part of the circuit, which proved dependable in stimulating pain of tracheobronchial origin.

Only the pharyngeal mucosa was anesthetized, utilizing 2 per cent pontocaine applied locally. No endotracheal anesthetic was given. After diagnostic exploration of the tracheobronchial tree, the long electrode was inserted through the bronchoscope. The mucosa was then stimulated at three sites: (a) the posterior wall of the right main bronchus, (b) the posterior wall of the left main bronchus, and (c) the posterior wall of the trachea approximately 1 cm. proximal to the carina (Fig. 3). During stimulation of a bronchus or of the trachea at the points just mentioned, the patient would locate the site of pain-sensation with the index finger. Following recovery from the procedure, the patients described the sensation as a moderately intense, "aching pain." They were able to localize this pain to areas as small as 2 or 3 cm. in diameter. In each instance, immediately following the bronchoscopy these areas were charted on prepared diagrams (Fig. 3).

RESULTS AND DISCUSSION

The aforementioned procedure was performed on twenty-five patients. The principal findings are presented in Fig. 4. Each point on the diagram represents the center of the area where pain was felt when the tracheobronchial mucosa was

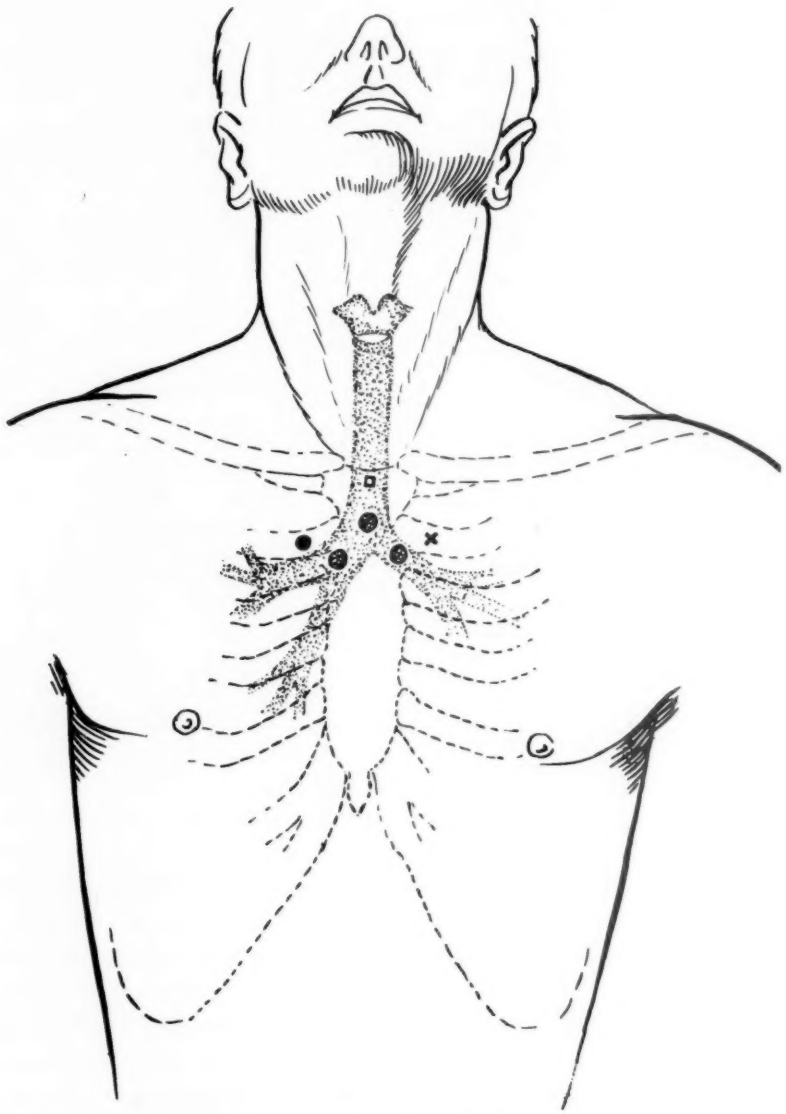

Fig. 3.—Diagram showing the response of a typical patient to electric stimulation of the trachea and the main bronchi. In all patients, the posterior wall of the tracheobronchial tree was stimulated at the points indicated by the large circles. The small black dot represents the localization of the pain in the anterior chest wall produced by stimulation of the right main bronchus; the small hollow square represents pain from the trachea, and the cross, pain from the left main bronchus.

stimulated. The solid black circles represent the localization of pain referred from the right main bronchus; the crosses, pain from the left main bronchus; and the hollow squares, pain from the posterior wall of the trachea.

Analysis of the diagram reveals that this referral of bronchial pain is consistent and symmetric on the homolateral side, and is confined to within 4 cm. of the sternum. Stimulation of the trachea resulted in pain felt in the midline.

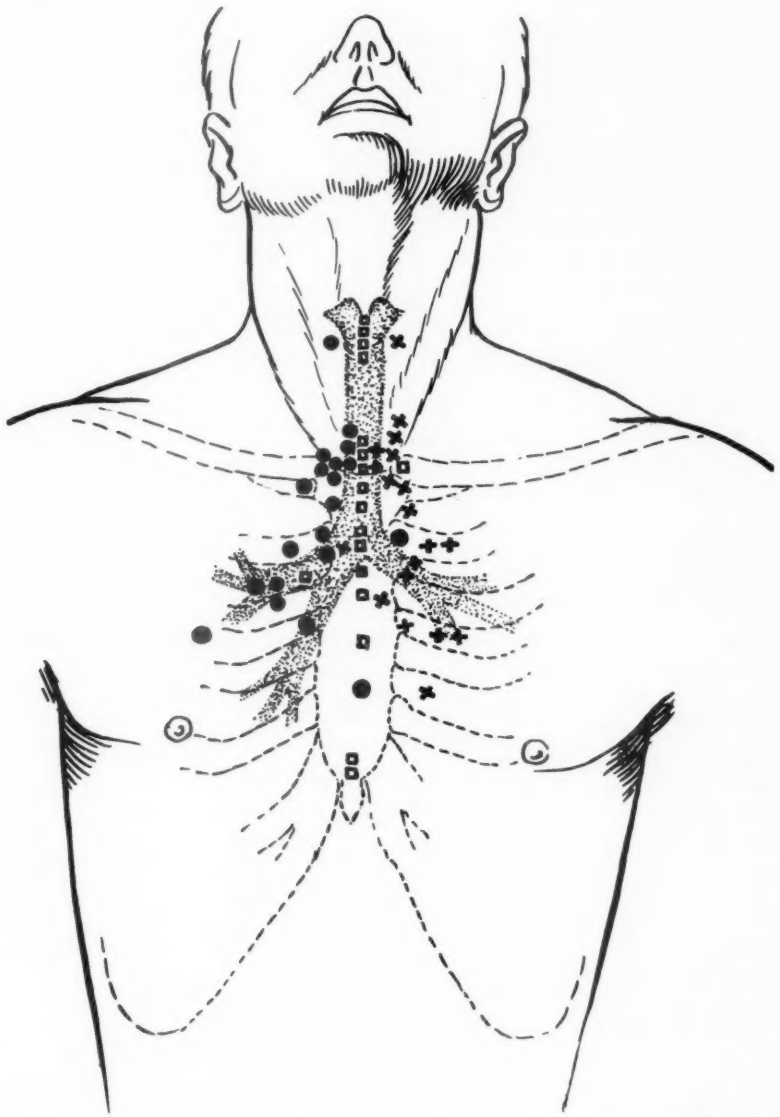

Fig. 4.—Localization of pain in the anterior chest wall produced by electric stimulation of the posterior wall of the tracheobronchial tree at sites indicated in Fig. 3, in a series of patients.

It can be seen from an examination of the diagram (Fig. 4) that not all tracheobronchial pain is substernal, but in many instances is referred to the suprasternal notch, and in some cases as high as the larynx.

Further studies are being made in an attempt to delineate the nervous pathways which transmit this sensation of pain to the central nervous system.

SUMMARY

1. A review of the early as well as the current literature pertaining to the afferent innervation of the lungs and respiratory tree reveals that the present clinical concept of the existence and localization of human tracheobronchial pain is not well defined.

2. Electric stimulation of the tracheobronchial mucosa accomplished during bronchoscopy indicates that the linings of the trachea and bronchi are sensitive, and that pain results.

3. The areas in which pain of tracheobronchial origin is felt have been charted. In general, pain arising from the bronchial tree is referred to the homolateral anterior chest within 2 to 4 cm. of the sternum, or to the anterior cervical region within 2 cm. of the midline. Pain of tracheal origin is felt in the midline anteriorly, at sites extending from the larynx to the xiphoid process.

4. Further studies are being made in an attempt to establish the afferent nervous pathways which transmit the sensation of tracheobronchial pain to the central nervous system.

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BLOOD VOLUME STUDIES IN THE DEPLETED SURGICAL PATIENT; CLINICAL APPLICATIONS

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THE marked susceptibility to shock resulting from minor trauma and blood loss in depleted soldiers with chronic wound infections was noted by Lyons[1] in 1943. He noted that this frequently occurred in the presence of normal hemoglobin concentration and found that these individuals had a diminished plasma volume, total red cell volume, and total blood volume, and an increased interstitial fluid volume. These observations led to further studies of blood volume in surgical patients depleted as a result of chronic infection, malignancy, and nutritional disturbances,[2] and to the postulation of the theory of "chronic shock."

Chronic shock was defined as a syndrome characterized by weight loss, diminished blood volume, increased interstitial fluid volume, and an increased susceptibility to shock from anesthesia or minor operative trauma. It was noted that individual variability in plasma volume resulted in frequent failure of the hematocrit, hemoglobin grams per cent, or red cell count to depict the true deficit of total circulating hemoglobin. It was found from blood volume studies before and after blood replacement that the individual's standard blood volume must be calculated on a basis of his optimal weight in health.

Patients were transfused to this level without significant hemoconcentration and maintained a standard blood volume when the primary cause of the depletion was eliminated. The preoperative restoration, by transfusion, of the depleted patients' blood volumes to normal for optimal weight and replacement of operative blood loss at the time of surgery resulted in the elimination of shock during major operations. Blood pressure remained remarkably stable during long procedures, and convalescence and return to optimal weight were hastened. Because of these results, we have continued to measure the blood volume in depleted patients and to restore their volumes to standard preoperatively.

METHOD

All determinations were made under fasting and resting conditions. As in previous studies,[2] the T 1824 (Evans blue dye) method was used in measuring plasma volume. Hemoglobin concentration was measured as oxyhemoglobin by a spectrophotometric method or by the $CuSO_4$ specific gravity method. The hematocrit value was measured by centrifuging blood in Wintrobe tubes at 3,000 r.p.m. for 30 minutes. Plasma protein concentration was measured by the $CuSO_4$ specific gravity or by the micro-Kjeldahl method. Calculations[4] for total circulating hemoglobin, total circulating plasma protein, total red cell

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volume, and blood volume were made from the above measurements of plasma volume and hemoglobin and plasma protein concentration. Deviations from "normal" were ascertained by comparisons with standards determined by Gregerson[4] using the same method. Mixing times were measured in several depleted patients and did not vary from those previously reported in "normals,"[5] and in certain cases with hypervolemia.[6] Therefore we have continued to use a mixing time of ten minutes.

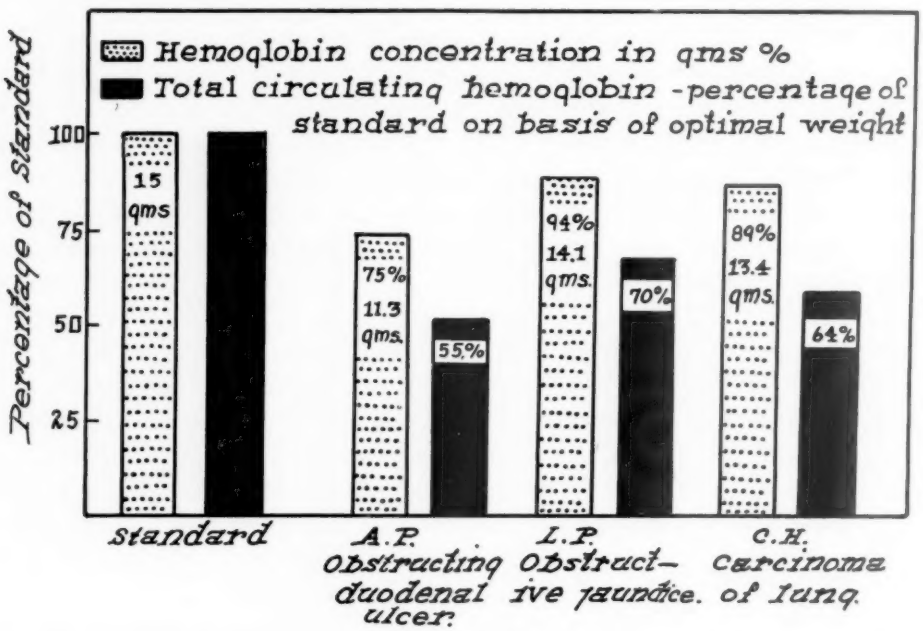

Fig. 1.—Hemoglobin concentration (Gm. per cent) versus total circulating hemoglobin.

RESULTS

We have conducted single or repeated blood volume studies on 145 depleted patients who had lost weight as a result of a variety of disease states, including malignancy, chronic sepsis, and functional or organic nonmalignant nutritional insufficiency. Included in the latter group were patients with complicated peptic ulcer, obstructive biliary cirrhosis, and partial chronic intestinal obstruction secondary to benign lesions. Determinations have also been made on seven patients with functional menorrhagia associated with weight loss.

Studies on patients with hyperthyroidism have not been included in the aforementioned series, as they have been previously reported,[3] although the findings were similar to those in other depleted patients. The patients are not presented according to groups because the illustrative cases hereinafter reported are representative of all patients studied regardless of the cause of depletion.

Hemoglobin Concentration Versus Total Circulating Hemoglobin.—With the few exceptions to be noted later, it was again found that depleted patients

possessed a significant decrease in plasma volume and blood volume. As illustrated in Fig. 1, this marked decrease occurred frequently in the presence of a near-normal hemoglobin concentration. Patients C. H., A. P., and L. P. in Fig. 1 had hemoglobin concentrations of 13.4, 11.3, and 14.1 Gm. per cent, respectively, amounts that would indicate need for little or no blood preoperatively. Inasmuch as their plasma volumes were low, however, they had measured total hemoglobin deficits of 330, 441 and 170 Gm., respectively. To restore their total circulating hemoglobin to "normal" for their optimal weight required approximately 2,200 c.c., 2,940 c.c. and 1,130 c.c. of blood, respectively. Reciprocal relationship between plasma and total red cell volume was not demonstrated. The low plasma volumes found resulted in a masking of hemoglobin deficits. The same lack of correlation between hemoglobin or red cell concentration and total circulating hemoglobin or red cell volume is again illustrated in Fig. 2. This patient, with a 42 hematocrit and a 14.1 Gm. per cent hemoglobin, had deficits of 305 Gm. of total hemoglobin and 1,030 c.c. of red cells. Thus he required over 2 L. of blood preoperatively to replace the total circulating hemoglobin and red cell deficit.

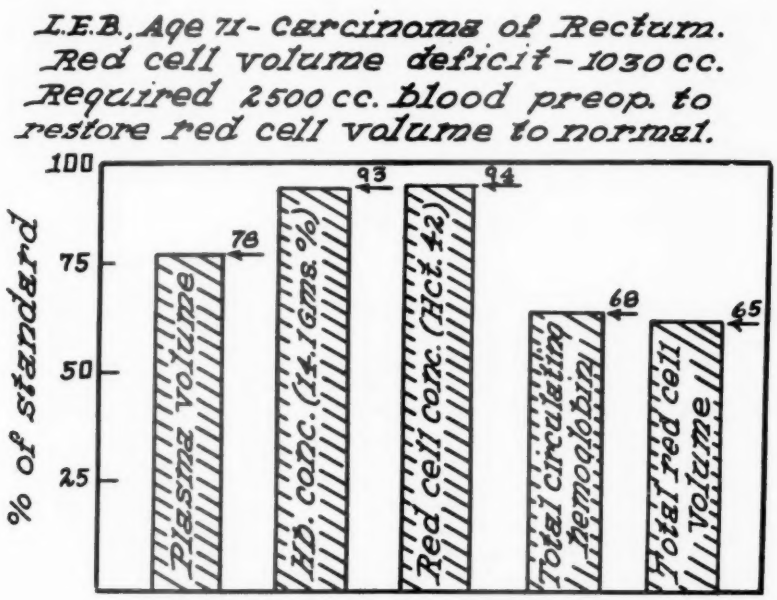

Fig. 2.—Hemoglobin and red cell concentration versus total circulating hemoglobin and total red cell volume.

Decrease in plasma volume in this group of depleted patients was present in all except eight patients with profound anemia. Three of these patients had carcinoma and five had persistent menorrhagia. All eight patients had a hemoglobin concentration of under 10 Gm. per cent. In the depleted group, a high preoperative plasma volume with hemoglobin concentration over 10 Gm. per cent was found in only one patient, who had marked bilateral hydronephrotic changes and probably had salt and water retention as a result of his renal dysfunction.

Plasma volume was not quantitatively related to the amount of weight loss. The tendency for the plasma volume to increase in extremes of anemia even if associated with weight loss is illustrated in Fig. 3. The level of hemo-

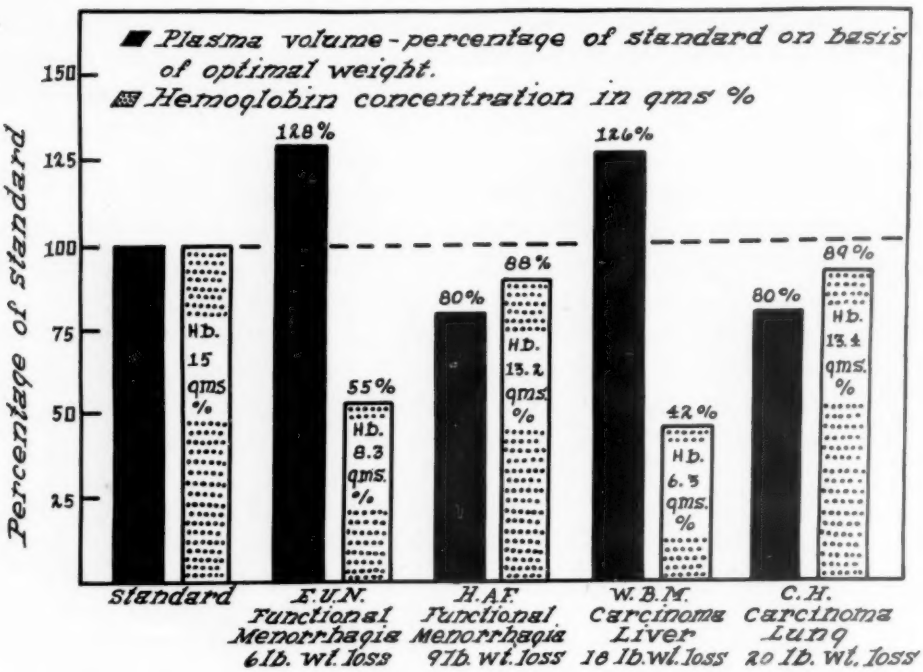

Fig. 3.—High plasma volumes in the occasional depleted patient with extreme anemia.

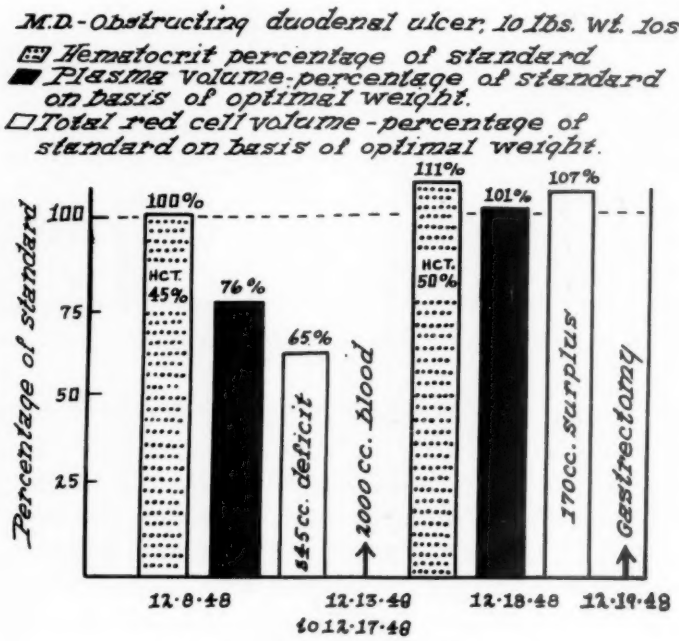

Fig. 4.—Replacement is quantitative.

globin concentration in depleted patients below which the plasma volume may revert to or above normal appears to be in the region of 10 Gm. per cent.

Although significant decrease in protein concentration in the patients studied did not occur, total protein was uniformly reduced because of reduced

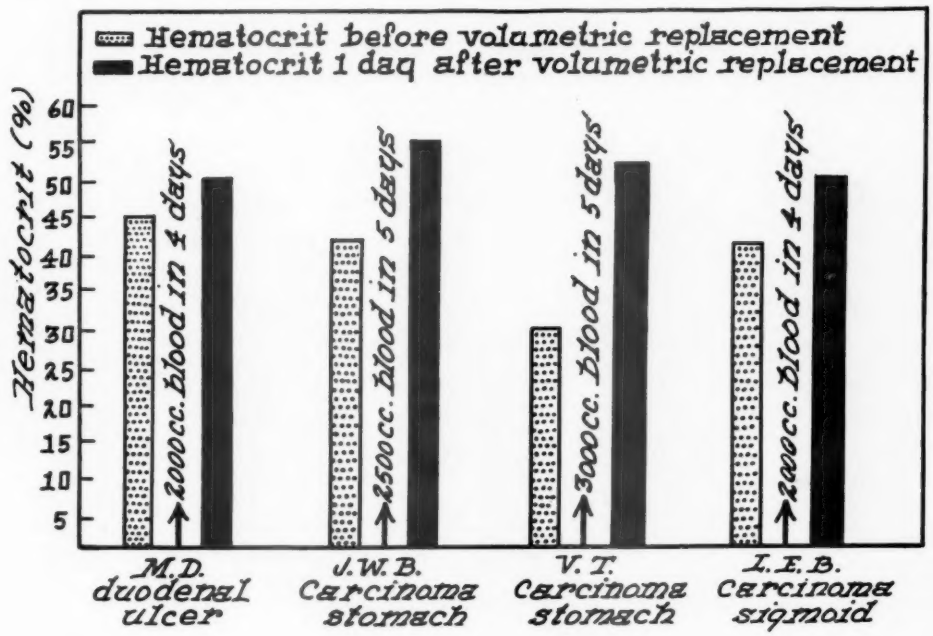

Fig. 5.—Lack of marked hemoglobin concentration with volumetric preoperative blood replacements in depleted patients.

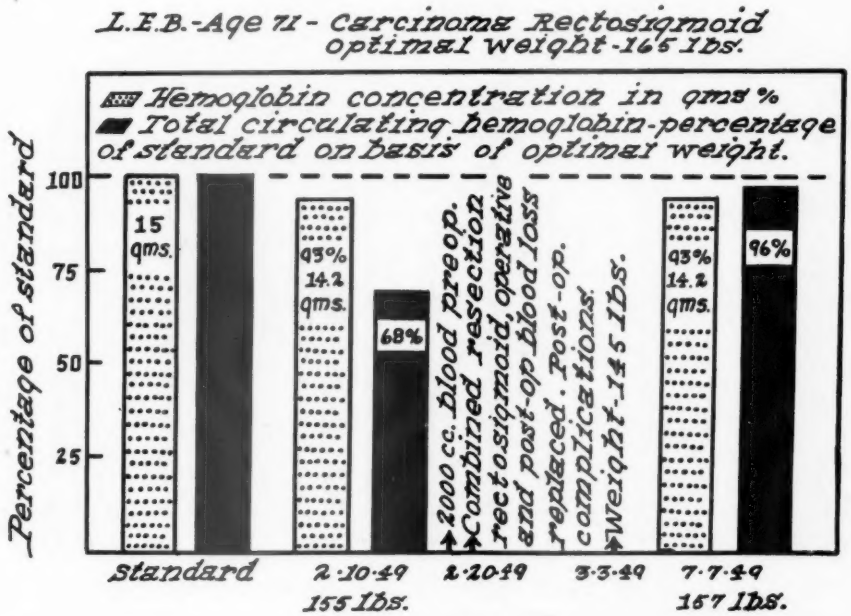

Fig. 6.—Postoperative maintenance of total circulating hemoglobin at standard for patient's optimal weight.

plasma volume. Fractional plasma protein studies were carried out in only a few cases.

Results of Hemoglobin Replacement.—The patients in this group coming to surgery were transfused in the immediate preoperative period at a rate of

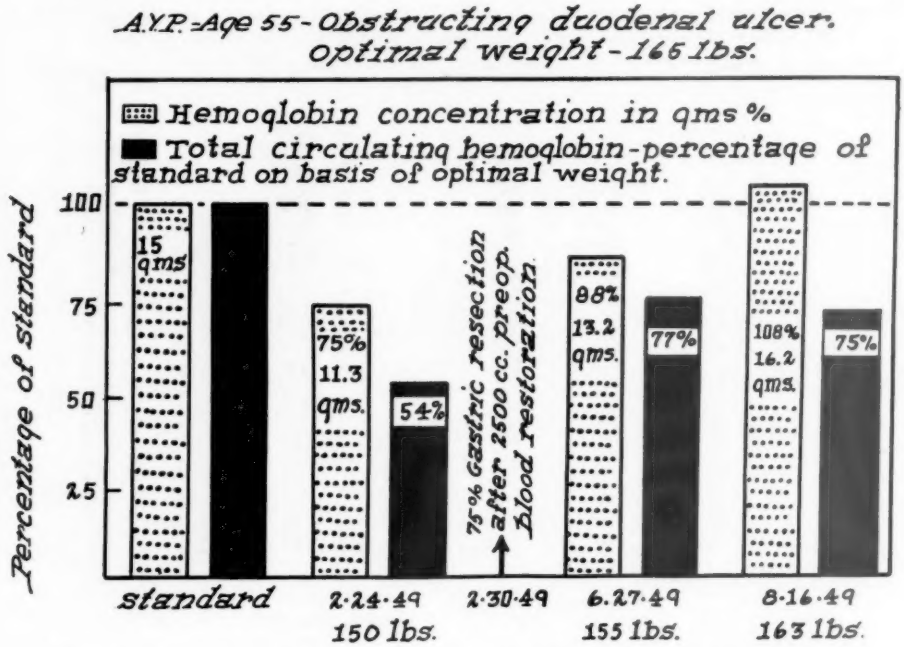

Fig. 7.—Slow hemoglobin replacement following extensive gastrectomy.

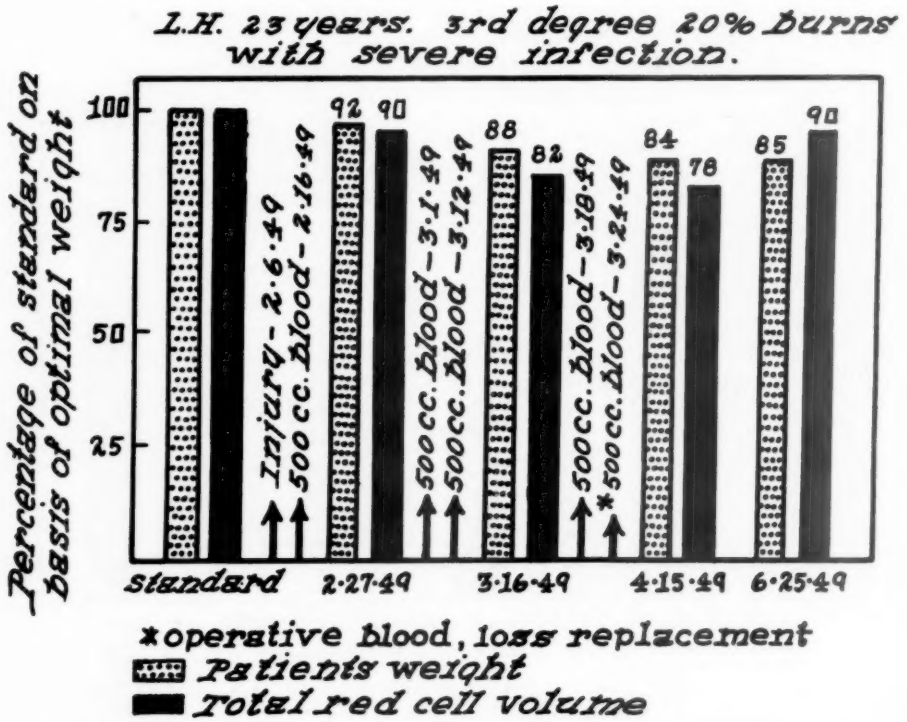

Fig. 8.—Progressive weight and red cell volume loss with severe infection.

500 c.c. to 1,000 c.c. of whole blood daily. No patient developed symptoms suggestive of cardiac overload. Blood volume determinations done after transfusion replacement of the measured total hemoglobin or red cell deficit again showed restoration of these components to standard for the patient's optimal weight, as illustrated in Fig. 4. This was not attended by significant hemoconcentration, as illustrated in Fig. 5.

Fig. 6 illustrates the maintenance of total circulating hemoglobin at "normal" for optimal weight following correction of the patient's pathologic state. Maintenance at this level occurred, as in previous studies, before complete restoration to optimal weight.

Fig. 8 represents the red cell volumes and weight of a patient with 20 per cent third degree burns who developed severe infection within ten days after burning. It is of interest that the cell volume and weight dropped in spite of 2,500 c.c. of whole blood replacement and a high protein intake, until the infection was finally well controlled on about the sixtieth day. This illustrates that prolonged maintenance of red cell volume cannot be expected from transfusion restoration in the presence of continued erythropoietic suppression secondary to infection.

CLINICAL APPLICATION

It is our policy in depleted surgical patients to restore the total circulating hemoglobin to "normal" in the immediate preoperative period and to replace operative blood loss at the time of surgery. In the postoperative period, effort is made to restore positive nitrogen balance by oral and/or jejunal protein administration and, when necessary, by the use of intravenous protein hydrolysates. Sufficient carbohydrate is given to spare the administered protein for the restoration of tissue, plasma, and enzyme protein, for the healing of the patient's wounds, and to replace protein loss from increased catabolism and losses from wound exudate.

We have been impressed with the stability of systolic and diastolic blood pressure and freedom from shock during extensive surgical procedures in properly restored patients. On a few occasions complete preoperative blood volume restoration has proved to be a valuable insurance during sudden massive operative hemorrhage. Postoperatively these patients have convalesced rapidly. Although nitrogen balance studies have not been done, early gain in weight exhibited by these patients during convalescence points to the fact that they were able to use their administered or ingested protein for restoration of body protein, once their pathology had been overcome.

We have also used blood volume studies to help in ascertaining the patient's nutritional status following extensive gastrectomy, inasmuch as failure to regain optimal weight is common following this procedure. Fig. 7 illustrates the marked total hemoglobin depletion persisting four months after 75 per cent gastrectomy. Blood volume studies following 50 per cent gastrectomy plus vagotomy[9] suggest that better maintenance of total circulating hemoglobin may result in patients with this operation than in patients with more extensive gastrectomy performed for ulcer. Only one case of postopera-

tive intravascular thrombosis occurred in this group. This took place three weeks postoperatively in a patient who was again anemic because of delay in regaining nutritional sufficiency following gastrectomy.

DISCUSSION

There is no reciprocal relationship between blood volume, hemoglobin concentration, and the amount of weight loss in the depleted patient. Thus estimates of preoperative blood needs cannot accurately be made without blood volume measurements. The preoperative administration of an arbitrary large amount of blood to the depleted patient frequently results in either insufficient replacement or in hypervolemia. Preoperative transfusion replacement to a point of hemoconcentration (that is, to a hematocrit of over 55 per cent) assures restoration of blood volume deficits. However, such management may result in hypervolemia and in blood waste. Only by blood volume measurement can deficits be accurately determined and corrected.

Our blood volume determinations have been performed in both the hospital and office laboratory. Teaching competent technicians the technique of performing accurate blood volume measurements has not been difficult. Maintenance of basal conditions for the test and clinical cooperation in accurately determining the patient's optimal weight are necessary. The equipment and materials necessary are available in the well-equipped laboratory, and the procedure is less difficult and time-consuming than many routinely performed blood chemistry examinations. We do not believe blood volume measurements too complicated for clinical adoption and recommended that they be done routinely in the depleted surgical patient.

In our experience, the T 1824 Evans blue dye method of plasma volume determination in depleted patients has measured with clinical accuracy variations from standards obtained by the same method. Determinations made after replacement of measured hemoglobin deficits correlate with the amount of hemoglobin administered. Significant hemoconcentration or evidence of overloading of the vascular system did not occur from volumetric replacement. Whether or not blood volume as calculated from plasma volume and the hematocrit measurement indicates actual blood volume, we do not know. We are convinced, however, that it does indicate accurately deviations from standard. The use of basal conditions minimizes errors inherent in the hematocrit determination. It has been suggested that variations in lymphatic flow might markedly interfere with protein-bound dye plasma volume determinations.[7] The average loss of lymph in a man with a severed thoracic duct is from 1 to 1½ c.c. per minute,[8] although this probably does not represent the total rate of lymph flow. It does not appear logical that sufficient variance in loss of albumin into the lymph would occur in the 10 minute mixing time to influence dye determinations significantly. We have noted no difference in the mixing curves in numerous depleted fasting patients from mixing curves of normal fasting individuals.

Volumetric replacement of measured blood volume deficit to standard for optimal weight in health does not cause significant hemoconcentration. Further,

following curative procedures which do not interfere with nutritional sufficiency, these patients maintain their blood volume at "normal" levels for their optimal weight. These findings demonstrate that the functional vascular capacity is proportional to the optimal, and not the actual, weight. Determination of optimal weight can usually be obtained from a carefully taken history. In rare extremes of height and weight and in the individual who, because of disease, has never attained optimal weight, estimates of individual optimal weight may be necessary.

In the previous discussion of chronic shock, it was postulated that decreased tissue elasticity due to protein depletion was the most important factor in causing decreased interstitial fluid pressure and shift of fluid from the vascular into the interstitial fluid compartment. An increased plasma volume was present in several depleted patients with extreme anemia and hemoglobin concentration under 10 Gm. per cent. This increase might be explained on the basis that sufficient depletion of hemoglobin may result in increased interstitial fluid volume, thus raising interstitial fluid pressure in spite of decreased tissue elasticity. This promotes increased fluid flow into the intravascular space with resulting increased plasma volume. The mechanism of such postulated interstitial fluid volume increase in extreme anemia could be explained on the basis of backward heart failure due to cardiac anoxia, or salt and water retention due to renal anoxia; however, clinical edema in this group has not been noted, and concomitant interstitial fluid volume studies in this group have not been done. Perhaps a more logical explanation lies in the limitations of the vascular capacity to remain constricted beyond a certain minimal point. As dilatation occurs, hydrostatic pressure drops, favoring ingress of fluid into the intravascular space and increasing plasma volume. Plasma volume increase does occur in convalescent depleted patients before complete restoration of weight, possibly because protein replacement and restoration of tissue elasticity occurs before restoration of the fat portion of the optimal weight.

Blood volume deficits in this depleted group of patients averaged about 2,000 c.c. Replacement of this amount of blood plus operative blood loss during surgery would be extremely difficult. Even though possible, operative replacement would not protect the patient from shock and anemic anoxia during the early operative period, nor would it make possible the reversal of anoxic changes in such organs as the liver in the preoperative period. Also, such rapid replacement of large volumes of blood during surgery would be expected to cause cardiac embarrassment in the older age group. The life span of the red blood cell is from 80 to 120 days. The life of the stored red blood cell may be significantly shorter.[11, 12] Further, the body normally destroys and resynthesizes hemoglobin at a rate of about 25 Gm. per day. If depression of erythropoiesis or increased cell destruction is present as a result of infection, malignancy, nutritional insufficiency, or other causes, anemia can develop rapidly. Further, restoration of total hemoglobin to

"normal" decreases the anoxic erythropoietic stimulus. For these reasons, we believe that blood should be given in the immediate preoperative period, preferably within several days preceding surgery.

Clinical results of complete preoperative and operative hemoglobin restoration continue to be very encouraging. We are convinced that the insurance against shock during surgery and the more rapid convalescence by complete restoration of hemoglobin make this procedure essential to the debilitated surgical patient. Our findings are in agreement with those of Stanton and associates,[9] that actual blood loss is often greater than the estimated operative and immediate postoperative blood loss. Replacement of actual postoperative blood loss is then also important in assuring that administered protein may be used for the important manufacture of proteins other than hemoglobin. It is also obviously important to maintain hemoglobin synthesis by supplying adequate protein and iron requirements in the postoperative and convalescent period.

Weight gain and absence of anemia are common indicators of nutritional sufficiency. Failure to gain weight following extensive partial gastrectomy, although frequently not associated with decreased hemoglobin concentration, is a common occurrence. It has previously been suggested[10] that such patients frequently have a significant decrease in their total circulating hemoglobin, and our studies to date tend to confirm this impression. We have found blood volume determinations of value in ascertaining the patient's postoperative nutritional status.

Restoration to, and maintenance of blood volume at, standard before, during, and following surgery results in prevention of shock. It also sets the stage for utilization of protein for rapid wound healing and early gain in weight and strength. These confirmatory follow-up studies argue for the measurement and volumetric replacement of blood volume deficits in depleted surgical patients. Determinations of blood volume deficits are not too difficult for adoption as a standard laboratory procedure. The effort necessary for establishment of the availability of such measurements is well repaid by the increase in the factor of safety for the debilitated surgical patient.

CONCLUSIONS AND SUMMARY

1. Measurement of blood volume by the T 1824 hematocrit method is essential for the determinaiton of transfusion requirements in the depleted surgical patient. The method is not too complex for clinical adaptation.

2. Plasma volume, hemoglobin, and plasma protein concentration were measured and blood volume, total circulating hemoglobin, total red cell volume, and total plasma protein were calculated in 145 depleted surgical patients. The T 1824 hematocrit method measures with clinical accuracy deviations from standards determined by the same method.

3. With a few noted exceptions, marked deficits of plasma volume, total hemoglobin, and red cell volume occurred in these patients. These deficits were frequently associated with normal or near-normal hemoglobin concentration.

4. It was again demonstrated that optimal weight forms an accurate basis for determining standard physiologic vascular capacity. The reasons for this are discussed.

5. An increased plasma volume was found in a few depleted surgical patients with a hemoglobin concentration under 10 Gm. per cent. Theoretical reasons for this finding are discussed.

6. Volumetric replacement of deficits by daily transfusions of whole blood in this group was carried out in the immediate preoperative period. Operative and postoperative blood losses were replaced by transfusion during and following surgery. The reasons for this method of management are discussed.

7. Volumetric replacement of measured blood volume deficits resulted in notable freedom from shock during or following surgery. Further, these patients gained weight and strength and their wounds healed rapidly. Routine measurement of blood volume in the depleted patient and volumetric preoperative replacement is advised.

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THE EFFECTS OF ABDOMINAL SURGERY UPON RENAL CLEARANCE

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INTRODUCTION

CERTAIN postoperative complications result from altered physiochemical balances elicited by the surgical intervention. Included in this type of complication are: wound disruption,[1] salt intolerance,[2] impaired gastrointestinal motility,[3] edema,[4] hypochloremia,[5] oliguria and anuria,[6] the hepato-renal syndrome,[7] and others. Some of these result from abnormalities of fluid, electrolyte, and oncotic balance. As the kidney is linked intimately with the maintenance of water and osmotic equilibrium, it is conceivable that alterations in kidney function might contribute toward the production of postoperative abnormalities. That operative intervention does produce changes in kidney function has been stressed by Smith.[8]

This study was undertaken accordingly to investigate renal function by measuring renal plasma flow, the rate of glomerular filtration, and the secretory ability of the tubules, and then to note what changes, if any, were induced by surgery. It is felt that an understanding of these alterations could serve to explain certain aspects of the postoperative metabolic irregularities, and possibly provide means for preventing and controlling them.

SUBJECTS AND METHODS

The subjects of this study are 12 patients who were admitted as candidates for gastrointestinal surgery. Five patients suffered from peptic ulcer, in 4 the diagnosis was gastric cancer, 2 had rectal carcinomas, and 1 patient suffered from chronic gastritis. The surgery consisted usually of resection of the involved organ. The types of operation, anesthesia, duration of operation, and other pertinent features pertaining to the surgical procedure are presented in Table I.† All patients were men, and their ages ranged between 50 and 71 years. None had known kidney disease. Though some of the patients presented moderate hypertension, none had manifestations of cardiac failure or cardiac dysfunction. The hemoglobin values of all patients except one (Patient 5) were normal when the renal function tests were performed.

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†One patient (O. T.), a 61-year-old woman, whose preoperative renal clearance studies were normal and who presented depression in all postoperative renal functions, is not included in the over-all evaluation of this data because during the postoperative studies her urine output was less than 1 ml. per minute.

In patients whose urine output is less than 1 ml. per minute, certain errors of emptying and timing might occur. Although these experiments utilized constant plasma levels of the chemicals for clearance studies which reduce the errors to a minimum,[9] the fact that this patient is the only one of the series whose urine output was so depressed makes it desirable to present the data separately.

The essential features of this case are as follows: A partial gastrectomy was performed for a gastric ulcer. The procedure was performed with nitrous oxide-ether anesthesia and lasted 5 hours. The lowest recorded blood pressure during surgery was 118/70. Preoperative blood pressure was 160/90 and postoperative value 150/90. She received 1,000 ml. of 5 per cent glucose in distilled water during the operation and the postoperative renal study was con-

Blood chemical studies of all patients were within normal levels except Patient 11, whose serum revealed hypochloremia pre- and postoperatively. The possible effects of hypochloremia upon renal function shall be discussed later in this presentation. During the preoperative test, the subject was maintained in a basal fasting state. Water was permitted ad lib. to insure adequate diuresis. An average daily intake of 3,000 c.c. of fluid was ingested. The preoperative test was performed from 2 to 3 days preceding surgery. During surgery the patients received dextrose in distilled water intravenously, and usually citrated whole blood transfusions. No intravenous saline solution was administered with the exception of Patient 2, who was given 500 c.c. of physiologic saline solution during the operative procedure.

The postoperative renal clearance tests were accomplished as soon after surgery as was technically feasible. An average period of 3.2 hours (ranging from 1.5 hours to 5 hours) (Table I) elapsed from the completion of the operation until the postoperative renal tests were performed.

METHODS

Kidney function tests were performed by the multiple period methods devised by H. W. Smith.[8, 11] Glomerular filtration rate was determined as the sodium thiosulphate clearance, and the effective plasma flow as the sodium para-aminohippurate (P. A. H.) clearance. Tubular function was studied by the saturation technique, that is, the maximal tubular secretory capacity for sodium para-aminohippurate (P. A. H.). Analyses were performed upon plasma filtrates according to the method of Fujita and Iwatake, and upon diluted aliquots of catheterized urine as described by Goldring and Chasis.[10] Para-aminohippurate was determined by the method described by Smith and associates.[11] Sodium thiosulfate was performed by the method of Gilman and co-workers.[12]

RESULTS

Table I summarizes the results of the various tests performed. (See footnotes, pages 716, 717, 718.) The values expressed usually represent the average of 3 clearance periods, except occasionally when technical difficulties precluded obtaining data for the 3 clearances. All results are corrected in proportion to surface area; the final figure is expressed in terms of the surface area of ideal man (1.73 square meters).

Effective Renal Plasma Flow.—The average effective renal plasma flow for normal males has been expressed as 697 (± 135.9 ml. per minute.[13]

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ducted 2 hours and 15 minutes subsequent to the operative intervention. There had been minimal blood loss. The data for the renal clearance are as follows:

EFFECTIVE RENAL PLASMA FLOW (ML. PER MIN.)		GLOMERULAR FILTRATION (ML. PER MIN.)		FILTRATION FRACTION		TUBULAR MASS TM (PAH) (MG./MIN.)	
PREOP.	POSTOP.	PREOP.	POSTOP.	PREOP.	POSTOP.	PREOP.	POSTOP.
649	310	120.2	60	18.5	19.4	78.3	61.7

She excreted 2,000 ml. of urine on her second day postoperatively. There was an uneventful convalescence, and she was discharged 6 days following operation.

The average preoperative values for the group reported in this series was 605.8 ml. per minute and varied from 433 to 778.6 ml. per minute.*

The average postoperative value was 608.9 ml. per minute, not significantly different from the preoperative figures. Although the average value revealed no significant alteration, there was considerable fluctuation among different patients (Fig. 1).

Five patients manifested depressions of the effective renal plasma flow (varying from 1.5 per cent to 38 per cent), while in 5 the plasma flow increased postoperatively. The reasons for the diverse response are not evident. The preoperative level apparently did not influence the values noted during the postoperative phase. Thus 1 patient (Patient 10) revealed the low preoperative

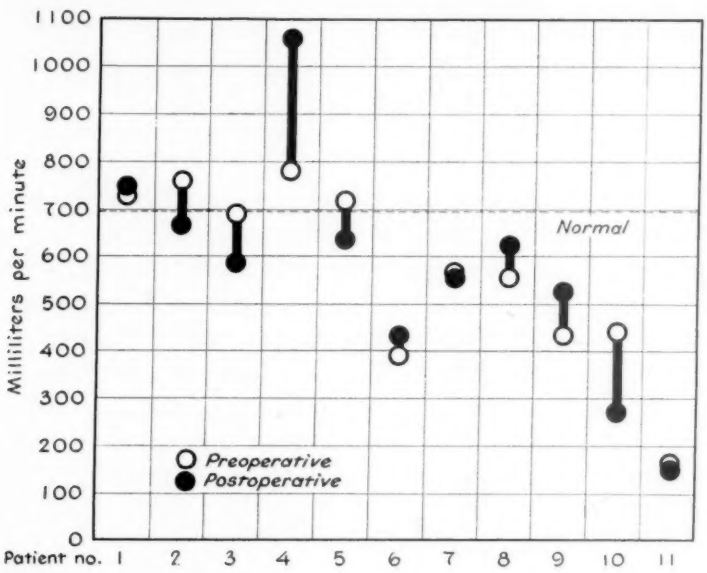

Fig. 1.—The effect of abdominal surgery upon effective renal plasma flow.

value of 443.2 ml. per minute, which dropped to the abnormally low value of 274.6 ml. per minute following a total gastrectomy. Patients 6 and 9, however, revealed rises in their plasma flow from low preoperative values. One case (Patient 4) demonstrated the high value of 773.6 ml. per minute during the preoperative state. At the time the test was performed the hemoglobin value

*The values for Patient 11 are not considered in the over-all adjudgement of the average figures because this patient suffered from hypochloremia during both the preoperative and postoperative studies. It has been demonstrated that hypochloremia produces alterations in renal clearances.[17]

The essential features of this case are as follows:

The patient was a 51-year-old man who suffered from adenocarcinoma of the stomach. Past history revealed numerous bouts of vomiting of 6 months' duration, with an associated 30 pound weight loss. Preceding surgery blood chemical studies revealed serum chloride 84 meq. per liter, carbon dioxide combining power 29 meq. per liter, serum sodium 147 meq. per liter, blood urea nitrogen 13 mg. per cent, hemaglobin 14.5 Gm. per cent, hematocrit 45.5 per cent red blood cells.

Immediately following surgical intervention, the serum chlorides had decreased to 65 meq. per liter, serum sodium to 125 meq. per liter. Intravenous therapy with normal saline solution increased the serum chloride to 95 meq. per liter 6 days later at discharge. The postoperative convalescence was uneventful.

It is interesting to observe that the general pattern of response to surgical intervention simulated the alterations activated by the surgical procedure in patients with normal plasma electrolytic balance and with increased kidney clearance values. Thus following surgery there was a slight increase in the filtration fraction and a depression of tubular excretion of para-aminohippurate.

was 9.1 Gm. per cent and the hematocrit was 23.7. Bradley and Bradley have demonstrated that anemia reduces the renal plasma flow in males by 25.2 per cent, and with recovery from anemia the decreased renal plasma flow remains depressed during the immediate recovery period.[14] It is interesting that our patient with severe anemia revealed the highest plasma flow in this series, which value was further increased during the postoperative state when the anemia had been corrected. The fact that the postoperative values recorded in this patient include also a correction from anemia introduces a variable which might vitiate utilizing the alterations in renal plasma flow as resulting exclusively from the surgical intervention. If this value is deducted from the over-all average change, the renal plasma flow reveals an average drop of 3.7 per cent; whereas if it is included the average postoperative change is + 0.5 per cent over the average preoperative value. Both alterations are insignificant.

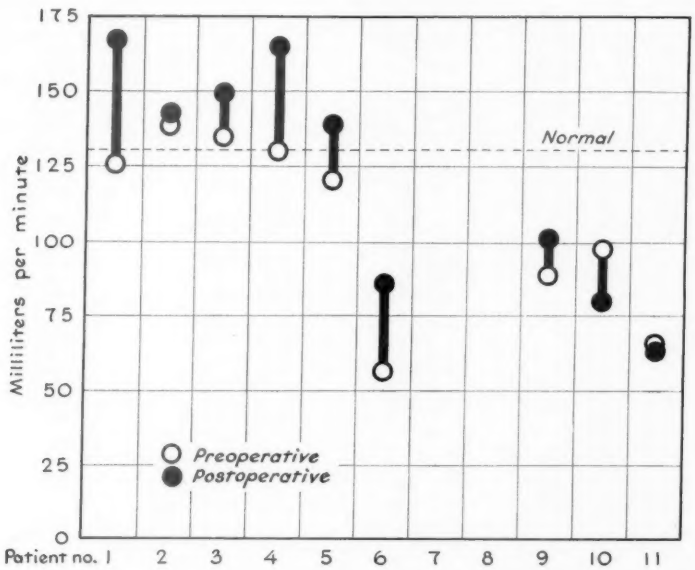

Fig. 2.—The effect of abdominal surgery upon glomerular filtration rates.

Glomerular Filtration Rate and Filtration Fraction.—The glomerular filtration rate in the preoperative studies averaged 114.3 ml. per minute. The normal value for males is reported as 131 (± 21.5) ml. per minute.[13]

The low value demonstrated in this series is not understandable. It is, however, significantly above a dangerous level, for the critical level of glomerular filtration rate for salt retention to occur has been reported in the vicinity of 70 to 80 ml. per minute.[16]

Following surgery there was an average increase in the glomerular filtration rate of 12.7 per cent, raising the average to 128.8 ml. per minute. An increase in filtration rate was observed in 7 of 9 cases in which the test was performed (Fig. 2).

The filtration fraction (the percentage of plasma filtered at the glomerulus) increased 17.4 per cent following surgery, the preoperative average value of

TABLE

PATIENT	AGE	SEX	DIAGNOSIS	OPERATION	DURATION OF OPERATION (HOURS)	ANESTHESIA	BLOOD LOSS (ML.)	FLUIDS ADMINISTERED: BLOOD (ML.)	FLUIDS ADMINISTERED: 5% GLUCOSE IN DIST. H_2O (ML.)	LOWEST BLOOD PRESSURE DURING OPERATION	PREOP. BLOOD PRESSURE
						OPERATION					
1. L. G.	50	M	Gastric ulcer	Subtotal gastrectomy & appendectomy	6	Nitrous oxide, curare, pentothal		1,000	1,000	128/7	05/7
2. L. A.	51	M	Duodenal ulcer	Subtotal gastrectomy	6.7	Nitrous oxide, ether	230	500	1,000 & 500 normal saline	110/6	10/8
3. W. M.	54	M	Gastric carcinoma	Subtotal gastrectomy & splenectomy	5.25	Cyclopropane, pentothal, ether	300	0	1,500	110/6	30/8
4. F. M.	58	M	Carcinoma of rectum with lung metastases	Colostomy	1.9	Nitrous oxide, ether		0	1,000	120/7	20/8
5. C. L.	56	M	Chronic gastritis	Subtotal gastrectomy	6	Pentothal, ether	138	0	1,000	100/7	05/6
6. F. K.	60	M	Gastric ulcer	Subtotal gastrectomy	5	Cyclopropane, pentothal, ether	45	500	1,000	96/6	00/9
7. E. O.	62	M	Gastric carcinoma	Subtotal gastrectomy	5.9	Cyclopropane, ether	600	1,500	2,000	105/6	40/8
8. H. O.	68	M	Gastric ulcer	Subtotal gastrectomy	5.5	Nitrous oxide, pentothal, curare	660	1,000	1,000	110/7	05/8
9. R. P.	71	M	Carcinoma of rectum	Abdominoperineal resection	6.5	Nitrous oxide, pentothal, curare	541	1,500	1,500	110/7	00/9
10. A. N.	62	M	Gastric carcinoma	Total gastrectomy	6.1	Cyclopropane, ether	100	1,000	1,000	70/5	00/7
11. B. B.	51	M	Gastric carcinoma	Subtotal gastrectomy	7.75	Ether	260	1,000	1,000	90/6	00/8

*The average values do not include Patient 11 (see text).

18.9 having mounted to 22.2 postoperatively. Seven of the 9 patients studied demonstrated an increase in filtration fraction (Table I).

Tubular Function.—The maximal rate of tubular para-aminohippurate excretion was observed in 6 patients. The normal value for males is described at 77.5 (± 12.9) mg. excreted per minute.[13] The average preoperative value of this series was 73.4 mg. per minute. This value decreased following surgery to an average of 66.5 mg. per minute, an average descent of 9.4 per cent. Three patients revealed no significant change while 3 others demonstrated noteworthy decreases (Table I).

LOWEST BLOOD PRESSURE DURING OPERATION	PREOP. BLOOD PRESSURE	POSTOP. BLOOD PRESSURE	HOURS FROM SURGERY TO POSTOP. TEST	RENAL CLEARANCE											
				EFFECTIVE RENAL PLASMA FLOW (ML/MIN.)			GLOMERULAR FILTRATION RATE (ML./MIN.)			FILTRATION FRACTION			TUBULAR EXCRETORY MASS (PAH) MG./MIN.		
				PREOP.	POSTOP.	% DIFFERENCE	PREOP.	POSTOP.	% DIFFERENCE	PREOP.	POSTOP.	% DIFFERENCE	PREOP.	POSTOP.	% DIFFERENCE
128/7	6/70	130/70	2	724.6	742.3	+ 2.4	126	167.3	+32.5	17.4	22.5	+29.2	80.7	66.4	–17.7
110/6	10/85	146/94	2.1	759	661	–13	138	142.4	+ 3.2	18.1	21.3	+17.7			
110/6	20/80	140/80	4.5	689	581	–15.7	134.1	149.1	+11.2	19.5	26.1	+33.8			
120/7	20/80	110/80	1.5	778.6	1,057.6	+35.9	130.2	164.8	+26.5	16.5	15.6	- 5.5	81.1		
100/7	05/65	110/65	2	717.6	634.3	–11.5	121	138.5	+14.5	16.9	21.9	+29.6	81.3	76.8	- 5.5
96/6	60/90	95/70	3.5	393.2	434.6	+10.5	57.3	86.4	+50.9	14.6	19.9	+36.3	66.6	50.2	–24.6
105/6	40/85	120/70	4.3	563	554.5	- 1.5	106.2			19.8					
110/7	05/80	140/70	4	557	622.3	+11.8	145.1			26.1			68.8		
110/7	80/90	176/70	4	433	527.3	+21.8	88	101.3	+15.7	21.6	19.2	–11.1	80.2	82.6	+ 3
70/5	50/70	140/100	5	443.2	274.6	–38	96.9	80.9	–16.5	18	31	+72.2	55.3	56.8	+ 2.7
90/6	05/80	100/70	4.5	169.4	160.2	- 5.4	64.6	64.2	0	38	40	+ 5.3	63.7	55.1	–15.6
	Average*			605.8	608.9	+ 0.5	114.3	128.8	+12.7	18.9	22.2	+17.4	73.4	66.5	- 9.4

DISCUSSION

These data demonstrate the wide fluctuation of renal response to surgery, including effects of anesthetic agents, preanesthetic drugs, and the defense mechanism of the body to surgical intervention. Smith aptly cautioned against studying normal kidney physiology upon operated anesthetized animals, and the data herein presented substantiate Smith's views.[8]

Before discussing the effects of surgery upon renal clearance it is interesting to notice the deviation from normalcy of kidney function in certain patients as they presented themselves for surgical intervention of gastrointestinal pathology.

TABLE I.

PATIENT	AGE	SEX	DIAGNOSIS	OPERATION	DURATION OF OPERATION (HOURS)	ANESTHESIA	BLOOD LOSS (ML.)	FLUIDS ADMINISTERED		LOWEST BLOOD PRESSURE DURING OPERATION	PREOP. BLOOD PRESSURE
								BLOOD (ML.)	5% GLUCOSE IN DIST. H_2O (ML.)		
1. L. G.	50	M	Gastric ulcer	Subtotal gastrectomy & appendectomy	6	Nitrous oxide, curare, pentothal		1,000	1,000	128/70	105/
2. L. A.	51	M	Duodenal ulcer	Subtotal gastrectomy	6.7	Nitrous oxide, ether	230	500	1,000 & 500 normal saline	110/60	110/
3. W. M.	54	M	Gastric carcinoma	Subtotal gastrectomy & splenectomy	5.25	Cyclopropane, pentothal, ether	300	0	1,500	110/60	130/
4. F. M.	58	M	Carcinoma of rectum with lung metastases	Colostomy	1.9	Nitrous oxide, ether		0	1,000	120/70	120/
5. C. L.	56	M	Chronic gastritis	Subtotal gastrectomy	6	Pentothal, ether	138	0	1,000	100/70	105/
6. F. K.	60	M	Gastric ulcer	Subtotal gastrectomy	5	Cyclopropane, pentothal, ether	45	500	1,000	96/60	160/
7. E. O.	62	M	Gastric carcinoma	Subtotal gastrectomy	5.9	Cyclopropane, ether	600	1,500	2,000	105/60	140/
8. H. O.	68	M	Gastric ulcer	Subtotal gastrectomy	5.5	Nitrous oxide, pentothal, curare	660	1,000	1,000	110/70	145/
9. R. P.	71	M	Carcinoma of rectum	Abdominoperineal resection	6.5	Nitrous oxide, pentothal, curare	541	1,500	1,500	110/70	190/
10. A. N.	62	M	Gastric carcinoma	Total gastrectomy	6.1	Cyclopropane, ether	100	1,000	1,000	70/50	130/
11. B. B.	51	M	Gastric carcinoma	Subtotal gastrectomy	7.75	Ether	260	1,000	1,000	90/60	120/

*The average values do not include Patient 11 (see text).

18.9 having mounted to 22.2 postoperatively. Seven of the 9 patients studied demonstrated an increase in filtration fraction (Table I).

Tubular Function.—The maximal rate of tubular para-aminohippurate excretion was observed in 6 patients. The normal value for males is described at 77.5 (± 12.9) mg. excreted per minute.[13] The average preoperative value of this series was 73.4 mg. per minute. This value decreased following surgery to an average of 66.5 mg. per minute, an average descent of 9.4 per cent. Three patients revealed no significant change while 3 others demonstrated noteworthy decreases (Table I).

TABLE I.

LOWEST BLOOD PRESSURE DURING OPERATION	PREOP. BLOOD PRESSURE	POSTOP. BLOOD PRESSURE	HOURS FROM SURGERY TO POSTOP. TEST	RENAL CLEARANCE											
				EFFECTIVE RENAL PLASMA FLOW (ML/MIN.)			GLOMERULAR FILTRATION RATE (ML./MIN.)			FILTRATION FRACTION			TUBULAR EXCRETORY MASS (PAH) MG./MIN.		
				PREOP.	POSTOP.	% DIFFERENCE	PREOP.	POSTOP.	% DIFFERENCE	PREOP.	POSTOP.	% DIFFERENCE	PREOP.	POSTOP.	% DIFFERENCE
128/70	105/70	130/70	2	724.6	742.3	+ 2.4	126	167.3	+32.5	17.4	22.5	+29.2	80.7	66.4	−17.7
110/60	110/85	146/94	2.1	759	661	−13	138	142.4	+ 3.2	18.1	21.3	+17.7			
110/60	130/80	140/80	4.5	689	581	−15.7	134.1	149.1	+11.2	19.5	26.1	+33.8			
120/70	120/80	110/80	1.5	778.6	1,057.6	+35.9	130.2	164.8	+26.5	16.5	15.6	- 5.5	81.1		
100/70	105/65	110/65	2	717.6	634.3	−11.5	121	138.5	+14.5	16.9	21.9	+29.6	81.3	76.8	- 5.5
96/60	160/90	95/70	3.5	303.2	434.6	+10.5	57.3	86.4	+50.9	14.6	19.9	+36.3	66.6	50.2	−24.6
105/60	140/85	120/70	4.3	563	554.5	- 1.5	106.2			19.8					
110/70	145/80	140/70	4	557	622.3	+11.8	145.1			26.1			68.8		
110/70	190/90	176/70	4	433	527.3	+21.8	88	101.3	+15.7	21.6	19.2	−11.1	80.2	82.6	+ 3
70/50	130/70	140/100	5	443.2	274.6	−38	96.9	80.9	−16.5	18	31	+72.2	55.3	56.8	+ 2.7
90/60	120/80	100/70	4.5	169.4	160.2	- 5.4	64.6	64.2	0	38	40	+ 5.3	63.7	55.1	−15.6
	Average*			605.8	608.9	+ 0.5	114.3	128.8	+12.7	18.9	22.2	+17.4	73.4	66.5	- 9.4

DISCUSSION

These data demonstrate the wide fluctuation of renal response to surgery, including effects of anesthetic agents, preanesthetic drugs, and the defense mechanism of the body to surgical intervention. Smith aptly cautioned against studying normal kidney physiology upon operated anesthetized animals, and the data herein presented substantiate Smith's views.[8]

Before discussing the effects of surgery upon renal clearance it is interesting to notice the deviation from normalcy of kidney function in certain patients as they presented themselves for surgical intervention of gastrointestinal pathology.

Four of the 10* patients studied revealed abnormally low effective renal plasma flow during the preoperative study period.

The exact mechanism responsible for the altered plasma flow is not discernible. The nature of the pathologic involvement apparently was not responsible because 2 of the 4 patients with benign lesions and 2 of 6 patients with cancer of the gastrointestinal tract revealed the diminished renal plasma flow. Blood pressure values were within normal limits and cardiac dysfunction apparently was not a contributory factor. Plasma protein values were within normal range in all instances. It is suggested that possibly anemia which had been rapidly corrected by transfusions in 3 cases could be a causative factor.[14] Plasma crystalloid studies revealed normal chloride and bicarbonate values in all instances, except Patient 11, who is presented separately because of a marked hypochloremia. In another study from this clinic, reductions in renal plasma flow and glomerular filtration rate have been demonstrated in patients who were hypochloremic. The renal abnormalities are corrected rapidly when a normal level for plasma chlorides is achieved.[17]

Renal Plasma Flow.—Postoperatively, although the average renal plasma flow did not change, a diminished flow did develop in certain patients. Diminution of renal plasma flow has been described in the following conditions: traumatic shock and blood loss[15, 18]; orthostasis[19]; chronic anemia[14]; Addison's disease[20, 21]; increased piezometric angle of the renal artery[22]; exercises[23]; injection of vasopressor drugs[8, 24]; increased abdominal pressure[25]; congestive heart failure[26, 27]; and others. Of this group, the important factors which could be considered as contributing to the observed changes during surgery are traumatic shock, acute blood loss, and increased abdominal pressure.

Depression of blood pressure was not the responsible agent because in most instances there was little difference in blood pressure during the pre- and postoperative renal clearance studies (Table I). A marked drop of blood pressure in Patient 10 during the operation was very likely a strong contributory factor for the depressed renal plasma flow postoperatively.

That blood loss was not the causative agent is indicated by the observation that the average blood loss of 9 patients as determined by the method of Baronofsky, Treloar, and Wangensteen[28] averaged 319.3 ml. Three patients who lost the greatest amount of blood (patients 7, 8, and 9) did not reveal a depression of the renal plasma flow postoperatively.

No significant increased abdominal distention occurred in these patients,[29] nor was there any alteration of the piezometric angle of the renal vessels in the operations herein described.[22]

It has been reported that no changes in renal plasma flow or glomerular filtration rate occur with ether anesthesia but that cyclopropane anesthesia does diminish the renal plasma flow.[33] No correlation was observed in this series between the type of anesthesia used and the observed postoperative renal function (Table I).

*Does not include Patient 11.

The liberation of adrenalin during surgery could possibly be a factor in reducing renal plasma flow, for this chemical, which is known to depress renal blood flow,[8, 24] has been shown to be liberated during the stress states.[30]

The significance of depressed renal blood flow has been commented upon frequently and in the absence of diminished blood pressure and diminished blood volume is interpreted to be indicative of intrarenal vasoconstriction which functions as a vascular buffer,[31] shunting blood to more vital structures and aiding to maintain arterial pressure.[8] Usually a decreased cardiac output incites the renal vascular constriction, but in other instances (arteriovenous fistula, beriberi, and chronic anemia) the instability of the arterial pressure has been interpreted to evoke the diminution in the caliber of the renal vasculature.[31, 32] Instability of arterial blood pressure is encountered frequently during surgery and may be one of the exciting factors producing a renal vasoconstrictive mechanism.

The reasons why certain patients developed conspicuous depressions in the renal plasma flow while others developed major increases remains enigmatic but does demonstrate the diverse nature of response of renal plasma flow to surgery.

Glomerular Filtration and Tubular Excretion.—The average changes postoperatively consisted of increased filtration rates with slight depression of the tubular excretion of para-aminohippurate (Tm PAH).

Filtration rate: The exact mechanisms whereby alterations in glomerular filtration rate occur are not understood completely. The rate does increase following intravenous administration of saline solution[35] and following the administration of desoxycorticosterone.[36] In patients with hypopituitarism the administration of adrenocorticotropic hormone (ACTH) produces a marked increase in glomerular filtration rate.[37]

Since none of the patients in this series, except 1, received saline solution, it is conceivable that the increased filtration rate might be associated with the liberation of certain intracorporeal hormones (possible adrenocorticotropin in response to surgical trauma—the alarm reaction of Seleye[39]). Depression of eosinophiles in the postoperative state favor this hypothesis.[40] Though the individual changes of glomerular function were not great, the general trend of the group does demonstrate an increased glomerular filtration rate (Fig. 2).

Filtration fraction: Associated with the average increased filtration rate an average increased filtration fraction was observed postoperatively. Although alterations in filtration fraction may be influenced by many factors (changes of permeability of Bowman's membrane, plasma protein oncotic pressure, blood viscosity, intrarenal tissue pressure), it is generally interpreted to represent changes of caliber of afferent and efferent renal arterioles.[34]

It may not be amiss to describe briefly these implications.

Filtration equilibrium is reached usually across the membrane of the glomeruli; hence, with a fall of both renal blood flow and filtration fraction it may be inferred that vasoconstriction has occurred at the afferent arteriole. Increase of filtration fraction with a correspondent decrease in renal blood flow associated with a decrease in filtration rate implies that both afferent and efferent

arterioles are in a constricted state. Under these conditions, if the increase in filtration fraction is proportionately greater than the decrease in blood flow, the denotation is that although both afferent and efferent arterioles are constricted, the efferent ones are constricted to a greater degree.

Since the filtration fraction was usually increased following surgery in this series, it may signify that arteriolar constriction had occurred, probably in response to some homeostatic mechanism elicited by surgery. In those instances where plasma flow was decreased and filtration fraction increased, it could signify that both afferent and efferent arteriolar constriction had occurred. As the degree of increase of filtration fraction exceeded that of plasma flow depression, it appears that the efferent constriction exceeded that of the afferent arteriole. However, in most of these cases, there was also an increase in the glomerular filtration rate, which increase may be completely independent of alterations of renal blood vessels and which could be the responsible agent producing the increased filtration fraction. Analyses of the data of Patients 2, 3, and 5, where decreased plasma flow was associated with increased glomerular filtration, revealed that the degree of diminution of plasma flow was greater in 2 of the 3 patients than the degree of increased glomerular filtration rate. In 1 patient (Patient 10) a decreased filtration rate accompanied a decrease in plasma flow with a resulting increased filtration fraction.

Therefore, in these cases the increased filtration fraction cannot be explained exclusively on the basis of increased filtration rate, but implies that intrarenal vascular spasm, more marked at the efferent arteriole, did contribute to the alteration. In 3 patients (Patients 1, 6, and 11) the increased filtration fraction appears to have been caused solely by an increased glomerular filtration rate.

Tubular mass: The decreased tubular mass demonstrates that in addition to variations of renal hemodynamics, alterations in the tubular transport mechanism also occur following surgery. Although studies of tubular reabsorption of glucose were not performed, the nature of the experiment would suggest that diffuse alterations of tubular cells occurred rather than destruction of nephrons.[8] Alterations in tubular excretion (Tm PAH) can occur in a great variety of conditions, among which are hormonal imbalance,[41, 42] hemorrhage and traumatic shock,[15, 18, 43] renal anoxia, [44, 45] poisoning with heavy metals,[46] and others. It is difficult to evaluate which factor or factors during surgery might have contributed to the depressed tubular excretion mechanism in this series.

CORRELATION OF RENAL CLEARANCE AND POSTOPERATIVE PHENOMENA

How to apply the aforementioned observations in interpreting certain postoperative complications introduces enchanting speculative avenues, but unfortunately the absolute mechanisms must await further experimentation.

Because a tendency toward oliguria or salt retention[2] could be a manifestation of kidney dysfunction, examination of the mechanisms concerned seems pertinent.

Several observers describe salt retention in heart failure as due to diminished glomerular filtration rate resulting in more abundant sodium retention.[26, 47]

Examination of their data reveals that the filtration rate after recovery of the heart failure when no edema existed paralleled the filtration rate during failure.[31] The opposite view, that increased reabsorption of sodium is a function of an increased glomerular filtration rate, has been claimed also.[48] The data, however, are not convincing. It appears accordingly that, although glomerular filtration rate may play a role in the production of salt retention other mechanisms also must function.

Since it is known that damaged tubular cells permit the reabsorption of abnormally large quantities of solutes delivered to them,[46] some investigators believe that the increased absorption of sodium and chloride by damaged tubular cells accounts for oliguria and edema.[49]

In this series the depression of tubular excretory mechanism was not striking and it appears unlikely that this factor is the cause for postoperative oliguria and tendency toward salt retention.

Although in a few cases in this series depressed renal blood flow, or in 1 instance decreased filtration rate (Table I), may account for a tendency for a depressed urine output, in most instances they could not be the accounting factors. It is postulated, therefore, that surgery, anesthesia, and/or the postoperative defense mechanisms of the body probably evoke a hormonal imbalance including possibly liberation of antidiuretic hormone.

In summary, these data do not support a hypothesis that ordinarily postoperative water and salt retention are the results of kidney damage or intrinsic renal dysfunction as measured by the methods herein described. In a few instances, especially when shock accompanies surgery, the renal dysfunction as manifested by depressed effective renal plasma flow and glomerular filtration rate probably contributes greatly toward the postoperative developments. In other instances transfusion reactions from the administration of incompatible whole blood may induce a lower nephron syndrome and anuria; a kidney damage may result from other causes, such as the hepato-renal syndrome.

Although renal damage apparently is not the cause for the usual postoperative alterations, the changes produced in kidney function during surgery give leads of extrarenal mechanisms which probably contribute to water and salt retention and other changes postoperatively. Thus the observed oliguria may be due to release of antidiuretic hormone.

Though studies have not been performed to document this hypothesis, it has been observed that strong stimuli for the production of antidiuretic hormone include morphine and barbiturates,[50] postural alterations,[51] and acetylcholine or stimuli evoking the production of acetylcholine.[50] Any of these factors may function during the operative period. Also fatty infiltration in the liver depresses urine output, presumably the effect of antidiuretic hormone,[52] and it has been demonstrated that a significant increase in the fat content of the liver occurs in human beings during abdominal surgical procedures.[53]

The decreased plasma flow and increased filtration fraction noted in some of the patients in this series could possibly be the result of adrenalin secretion,[8, 24] while increased plasma flow and increased filtration fraction noted in other

patients of this series might be manifestations of adrenocorticotropic hormone release which is known to produce those changes in certain conditions.[37] The probability is that a hormonal imbalance caused by surgery and reflected in kidney clearance tests contributes to certain postoperative phenomena. The degree of alteration varies in different patients.

CONCLUSIONS

1. Renal clearances of sodium thiosulfate and sodium para-aminohippurate were performed upon 12 patients before and after abdominal surgical procedures to study the effects of surgery (including anesthesia and preanesthetic drugs) upon renal function and to note if alterations in renal function contribute toward postoperative complications.

2. The preoperative studies revealed that certain patients with gastrointestinal pathology present depressed renal function (effective renal plasma flow and glomerular filtration rate), probably results of certain metabolic abnormalities (hypochloremia,[17] anemia,[14] and so on). There was no known cardiac or renal pathology in the patients with altered renal clearances.

3. Although the average postoperative changes in effective renal plasma flow (+ 0.5 per cent) is insignificant, certain patients demonstrated significant depressions in renal plasma flow, while others had a marked increase of renal plasma flow.

4. The glomerular filtration rate tended to increase after surgery (average + 12.7 per cent) and the filtration fraction tended to increase also subsequent to surgery (average + 17.4 per cent). The altered filtration fraction is due to vasoconstriction of renal efferent arterioles in certain instances and to increased glomerular filtration rate in others.

5. Surgery evokes a slight depression of tubular excretory mass (Tm PAH) (average decrease of 9.4 per cent).

6. Except in certain instances where shock or marked blood loss is associated with surgery and which result in severe alterations in kidney function (Patient 10, this series) postoperative alterations (oliguria) are not the results of kidney dysfunction as determined by the clearance techniques.

7. Certain patterns of changes in renal clearance subsequent to surgical intervention (decreased plasma flow and increased filtration fraction, or increased plasma flow and increased filtration fraction) are known to result from the administration of specific hormones (adrenalin in the first example or adrenocorticotropic hormone in the second example) and suggest that possibly hormonal alterations evoked by surgery and reflected in renal clearance studies contribute toward some of the observed postoperative metabolic irregularities (oliguria, tendency toward salt retention, or edema and others). The possibilities of these associations are discussed.

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PRESACRAL NEURECTOMY IN THE TREATMENT OF DYSMENORRHEA

A Report of 125 Cases

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DYSMENORRHEA affects approximately 25 per cent of all women to some degree between the ages of 14 and 40. Alleviation of this distressing physical, mental, and social handicap in this unfortunate group has long been a challenge to the medical profession. With the advent of large numbers of women in business and industry during the war years, the effective treatment of dysmenorrhea became a matter of considerable economic importance and interest in the problem was generally stimulated, resulting in numerous contributions to the literature.

Numerous therapeutic agents and measures have been devised in an effort to control dysmenorrhea but few have proved to be of more than limited value. Symptomatic therapeusis with analgesic, antispasmodic, and sedative drugs is palliative at best. Endocrine therapy, although theoretically sound, has been disappointing. Cervical dilatation and uterine suspension relieve only a limited number of cases. Elimination of pelvic pathology does not always result in a cure. Psychotherapy is efficacious only in selected cases. Presacral neurectomy and ovarian denervation are of value only in cases of primary uterine and primary ovarian dysmenorrhea respectively. Finally, panhysterectomy and castration seem to be the only recourse in certain cases. The limited value of each of these measures attests to the wide variety of pathologic conditions that may underlie this symptom and obviously, in the light of our present knowledge of the etiology of dysmenorrhea, there can be no single satisfactory approach to the problem. Each case must be accurately diagnosed, carefully evaluated, and then the proper specific treatment employed.

Dysmenorrhea is generally classified as primary or functional when no gross pelvic pathology is evident and secondary when it is associated with some demonstrable pathologic process in the pelvis or pelvic organs. The primary type has been subdivided into primary uterine dysmenorrhea and primary ovarian dysmenorrhea. The pathology underlying the primary types has not been completely clarified; however, there is increasing evidence that it may be confined to the intrinsic or extrinsic sympathetic systems of the uterus and ovaries. Whether the sympathetic system is primarily concerned because of a pathologic process involving it, or is only secondarily concerned because of the afferent and efferent impulses it transmits, it would seem that the logical direction of therapeutic or symptomatic attack would be toward the surgical interruption of this system since a high percentage of "clinical cures" can be effected without compromising the physiology of the urogenital organs. On the other

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hand, secondary dysmenorrhea can be reasonably attributed to such pathologic conditions as cervical stenosis; retrodisplacement of the uterus; uterine, adnexal, and ovarian tumors of any type; pelvic inflammatory disease; endometriosis; adhesions; and so on, and the dysmenorrhea can frequently be relieved by the elimination of the pathology concerned. Theoretically, at least, such a classification provides a simple clear-cut basis for the proper diagnosis and selection of cases. Clinically however, differentiation may be quite difficult, for doubtless primary and secondary dysmenorrhea exist concurrently at times and no doubt primary dysmenorrhea exists in the presence of asymptomatic pelvic pathology occasionally. Therefore one cannot always be dogmatic in the classification of dysmenorrhea, and such combinations doubtless account for some of the failures encountered with the various methods of specific treatment.

Excellent discussions of the anatomy and physiology of the superior hypogastric plexus as well as the historical and technical aspects of presacral neurectomy can be found in the publications listed in the accompanying bibliography and further reiteration of this material is considered beyond the scope of this brief report.

The purpose of this paper is twofold: primarily, to report the results of 125 cases of intractable dysmenorrhea treated by resection of the superior hypogastric plexus alone, or combined with corrective pelvic surgery, and secondarily, to focus attention again on the procedure known as presacral neurectomy, which was introduced by Cotte nearly 25 years ago. This operation has produced uniformly good results in the treatment of primary uterine dysmenorrhea and has been gratifying in a high percentage of carefully selected cases with pelvic pathology.

The successful results of this operation depend upon the careful selection of cases and the complete excision of the superior hypogastric plexus. Few, if any, failures should be encountered in true primary uterine dysmenorrhea. An analysis of the "failures" reported in the literature following presacral neurectomy for secondary dysmenorrhea reveals that the majority of these cases fell into one of the following 3 categories: (1) those with psychoneurotic backgrounds who responded poorly to psychotherapy, (2) those in which considerations of age, child-bearing, or other factors temporized the surgeon's decision to perform radical surgery for endometriosis or chronic pelvic inflammatory disease, and (3) those in which subsequent surgery revealed incomplete resection of, or reconstitution of, the superior hypogastric plexus.

RESULTS

For convenience of comparing this report with previous reports, all cases in which no gross pelvic pathology other than a physiologic retrodisplacement of the uterus could be found are classified as primary dysmenorrhea. All other cases are classified as secondary dysmenorrhea, although we feel that some of these cases may be ones of true primary uterine dysmenorrhea superimposed on asymptomatic pelvic pathology or mixed types. All of these cases gave histories of severe incapacitating dysmenorrhea for periods of 6 months or longer, and all had failed to respond satisfactorily to conservative measures of treat-

ment. The conservative measures routinely used consisted of the correction of hygenic deficiencies, the use of mild antispasmodic, analgesic, and sedative drugs, and psychotherapy as indicated. Endocrine therapy and cervical dilatation and curettage were used in selected cases as indicated. Spinal anesthesia was used in all cases and at surgery, the appendix and gross pelvic pathology were removed routinely. Retrodisplaced uteri were suspended by the Mayo-Barrett or Norris technique in the majority of cases.

A review of the records of 125 consecutive cases of intractable dysmenorrhea treated by presacral neurectomy during the period January, 1942, to January, 1949, at the St. Therese Hospital, Beaumont, Texas, by the senior author, revealed that 80.4 per cent were of the primary type of uterine dysmenorrhea and that the remainder had sufficient pelvic pathology to warrant a diagnosis of either true secondary or mixed type of dysmenorrhea. It was not felt that any cases of true primary ovarian dysmenorrhea were recognized as such; however, such a diagnosis might explain some of the failures. The average age of onset in the primary uterine dysmenorrhea group, of which 92 per cent were married, was 14 years. In the acquired group, of which 96 per cent were married, the average age of onset was 25 years. It is of interest that 49 per cent of the primary group in this series had borne children either during, before, or after the development of dysmenorrhea. This fact does not support the concept that childbirth is an effective treatment of primary uterine dysmenorrhea.

The psychoneurotic factor was of sufficient degree to warrant special psychotherapeutic measures in 1 case of the primary group and in 1 case of the secondary group. Of the 2 failures, both were moderately severe psychoneurotics.

Cervical dilatation for 2 days prior to several consecutive menses was attempted in 80 per cent of the cases without producing more than temporary beneficial results. In a few of the cases partial relief was obtained for 2 to 3 months.

Endocrine therapy was administered in 90 per cent of the primary group and in 75 per cent of the secondary group. Approximately one-half of this group received 6.0 to 10 mg. of diethylstilbesterol daily for the first 14 days of several consecutive cycles and the remainder received 5.0 mg. progestin every other day for 1 week proceeding the onset of several consecutive periods. This treatment failed to produce sustained satisfactory results in this series.

In the secondary dysmenorrhea group evidence of chronic pelvic inflammatory disease was present in 75 per cent of the cases. Varying degrees of endometriosis were found in 20 per cent of the secondary group. Only those cases in which the endometrial implants were removed without sacrificing the uterus are included in this series.

All grossly pathologic ovaries with the exception of those containing simple cysts alone were removed. Oophorectomy or salpingo-oophorectomy was performed in 71.4 per cent of the cases of secondary dysmenorrhea. Uterine suspension of the Mayo-Barrett or Norris type was performed in 48 per cent of the cases of primary dysmenorrhea and in 58 per cent of the secondary group. Appendectomy was performed routinely. The appendix had been removed at previous operation in 17 per cent of the total series. Eight patients under

observation and treatment for primary dysmenorrhea and 3 patients under treatment for secondary dysmenorrhea developed appendicitis. Presacral neurectomy was performed at the time of appendectomy in all of these cases. In each case, the appendix was acutely or subacutely involved on microscopic examination, but there was no gross evidence of peritonitis or external exudate.

There were no significant postoperative complications in this series. A sanguinous cervical discharge was noted during the immediate postoperative period in 18 per cent of the cases. There have been no adverse changes in the bowel or urinary habits of any of the patients. Approximately 60 per cent have noted improvement in the regularity of the menstrual cycle and none have noted any adverse changes. None of the cases have noted a decrease in libido; however, 20 per cent have felt that there has been a definite improvement in that respect. Normal pregnancies and deliveries have occurred subsequent to operation in 38 per cent of the total series and there has been no increase in the expected incidence of miscarriage in the group.

Complete relief from dysmenorrhea has been experienced by 88.5 per cent of the patients with primary dysmenorrhea since operation, whereas only 75 per cent of the patients with secondary dysmenorrhea have been free of pain. A decrease in both the degree and duration of dysmenorrhea to the extent that the patients were no longer confined to bed or otherwise incapacitated during their regular period was noted by 8.62 per cent of the primary group and 20 per cent of the secondary group. Less than 50 per cent improvement was considered a failure in this series and 3.88 per cent of the patients with primary dysmenorrhea and 5 per cent of the patients with the acquired type fell within this group. Hysterectomy has subsequently been necessary in 4 of the cases of the total series for the following reasons: (1) widespread endometriosis with chronic pelvic inflammatory disease; (2) pelvic inflammatory disease (developed after presacral neurectomy was performed); (3) fibroids; and (4) dermoid cyst (bilateral).

One of the "failures" in the primary dysmenorrhea group had immediate and complete relief for 4 months. Beginning with the fourth menstrual period postoperatively, she began to experience dysmenorrhea which increased with each subsequent period until bed rest was required during the eighth period. She was given 10 mg. progesterone every other day for 1 week prior to onset of menses plus ¼ gr. phenobarbital 3 times a day. Since the second period following this therapy she has experienced almost complete relief.

SUMMARY

The acceptance of presacral neurectomy as a sound treatment for intractable dysmenorrhea has been very slow in this country, as evidenced by the relatively small number of cases that have been reported by our foremost clinics and medical centers. The rigid criteria that have been widely adopted for the selection of cases are unquestionably justified, for the technical difficulties are few and the incidence of dysmenorrhea is high, which invites abuse of this procedure. There is no question, however, that in carefully selected cases of both primary

and secondary dysmenorrhea this operation will result in a high percentage of complete cures and in this group of cases it is the treatment of choice, as no other treatment can offer as much to these patients.

It has been reported that presacral neurectomy is of value and should be done frequently in cases of endometriosis where dysmenorrhea is the presenting symptom. In view of the limited distribution of the fibers of the superior hypogastric plexus and the ovarian sympathetic system, one cannot reasonably assume that dysmenorrhea results from distant endometrial implants when such cases are cured by presacral neurectomy. The question arises whether endometriosis, per se, causes dysmenorrhea or whether primary uterine dysmenorrhea and endometriosis exist concurrently in certain cases according to the law of chance. However the cases may be, the surgeon's judgment in the employment of radical surgery for the treatment of endometriosis should not be tempered by the apparent success of presacral neurectomy in some of these cases.

In view of the high incidence of failures following the elimination or correction of pelvic pathology alone in cases of severe secondary dysmenorrhea as compared to the favorable results reported when these procedures are combined with presacral neurectomy, and in view of the neglible adverse effects associated with this latter procedure, we feel that presacral neurectomy should be routinely done in a large percentage of these cases.

CONCLUSIONS

1. Presacral neurectomy is the treatment of choice in properly selected cases of primary uterine and secondary dysmenorrhea.

2. Adverse postoperative sequelae following presacral neurectomy are negligible.

3. Presacral neurectomy should be weightily considered in all cases of secondary dysmenorrhea submitting to surgery for correction of pelvic pathology.

4. The success of the operation depends on the proper selection of cases and the complete resection of the superior hypogastric plexus.

5. The morbidity and mortality rate following this operation should be minimal.

6. One hundred and twenty-five cases of intractable dysmenorrhea treated by presacral neurectomy are reported.

ADDENDUM

Since this report was written an additional 25 cases of intractable dysmenorrhea have been treated by presacral neurectomy and have been followed for a minimum of 3 months. Twenty of these were of the primary type and 5 were of the secondary type. There were no failures in this primary group. None have complained of any adverse sequelae and only 1 of the secondary group has failed to experience complete relief. She states that she is between 50 per cent and 75 per cent improved.

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PLATEAU FRACTURES OF THE TIBIA

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A PLATEAU fracture is a fracture of the proximal end of the tibia, usually involving an articular surface. It is the result of a crushing injury produced by the impact of the femoral condyle against the corresponding tibial plateau and was first described in the literature by Thamhayn, in 1852. Associating this type of fracture with injury caused by the impact of an automobile bumper on the lower leg, Cubbins and associates used the term "bumper fracture." Cotton and Berg described the same fracture as a "fender fracture." Since "bumper fracture" is also used to describe a fracture of the middle and upper one-third of the tibia, some confusion in terminology has resulted. A more specific term would be "plateau fracture." This fracture is regarded as serious as it involves a major weight-bearing joint and loss of function results in a high percentage disability of the extremity.

ANATOMY

The knee joint is the largest and one of the strongest joints in the body, this latter fact being shown by the rarity of knee joint dislocations. It consists of two condyloid joints (between femoral and tibial condyles) and an arthroidal joint (between patella and femoral condyles). The great stability of the joint is due to the multiplicity and strength of the intra- and extra-articular ligaments and to the muscular attachments, while the greatest weakness of the joint is the expanded cancellous condyles poorly supported by the relatively narrow tibial shaft. This condition, together with the strength of the tibial and fibular ligaments, and the density of the femoral condyles, accounts for the likelihood of fractures in this region involving the tibial plateau. The greater weight-bearing force is distributed through the medial femoral condyle to the medial plateau; consequently, when this plateau is involved, a greater disability is to be anticipated.

MECHANISM OF INJURY

Injury to the tibial plateau is the result of either or both femoral condyles being directed against the corresponding tibial condyle or condyles, which may be either crushed or split from the tibial shaft. Violence may be either direct or indirect in nature. By the former mechanism, a force is directed to a point at or just below the knee with the leg fixed on the ground, causing a forced genu valgum. This results in a downward force of the relatively dense lateral condyle of the femur against the cancellous portion of the tibial plateau. This fracturing force is increased by the leverage effect of the resisting medial collateral ligament. The plateau may be split and displaced downward and outward, or

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may be comminuted and depressed. By the indirect mechanism, the force is transmitted in the long axis of the femur through the femoral condyles to the tibial plateaus. With the leg in abduction the greater force is exerted on the lateral plateau and is relatively increased when the medial collateral ligament remains intact. Conversely, the force is distributed to the medial plateau when the leg is in adduction. The fracturing force to the tibial plateau is reduced when there is a concomitant rupture of the opposite collateral ligament.

In our series of 111 cases, lateral plateau fractures were approximately twice as common as the other types. Thus, the lateral plateau was involved in 65 per cent of the cases, the medial plateau in 21 per cent, both in 9 per cent, and the fracture was intercondylar in 5 per cent of the cases. Direct violence accounted for the injury in 63 per cent of the cases, indirect violence in 34 per cent, while 3 per cent awakened from alcoholic state to discover fractures of unaccountable origin. Proportionately, there were more lateral plateau injuries with direct violence than with indirect violence, while there was little difference in the proportion of fractures of the medial plateau in the two mechanisms of injury. Four of our five cases of intercondylar fracture were the result of indirect violence while all nine cases of bilateral plateau involvement were from direct violence.

ETIOLOGY

The most common cause of a plateau fracture is the result of direct trauma by an automobile, which accounted for 50 per cent of the injuries in our series. The next most common cause in our group of cases was indirect trauma in the form of a fall, either at home or in the street, which was usually accompanied by a twisting motion at the knee, accounting for 20 per cent of the injuries. The remaining 13 per cent, due to direct injury, followed blows in the region of the knee, such as being kicked or struck by a blunt instrument. Ten per cent of the fractures resulted from a fall from a height. In three instances the plateau fracture resulted from injury received as the individual was thrown from a moving vehicle; in three others the manner of injury was unknown, the individuals having a history of alcoholism. One case sustained a lateral plateau fracture upon being struck by a bicycle, while in another instance a plateau fracture occurred as a result of a fall injuring a Charcot joint. In one of our cases a 32-year-old man, having no antecedent trauma, experienced sudden onset of severe pain in the knee while walking. X-ray examination revealed the presence of a linear fracture of the medial condyle without displacement. This may be considered to fit into the category of "march fracture of the tibial plateau," sixty-four cases of which were reported in 1946 by Levitin. He defined it as a transverse linear fracture of the tibial plateau with no evidence of definite antecedent trauma, the injury frequently occurring in soldiers after long hikes, and becoming manifest by pain without limitation of motion of the knee. In his series the medial condyle was more frequently involved than the lateral in the ratio of 2.6 to 1. Increased incidence of medial condylar involvement in this type injury might be expected in view of the fact that a greater share of body weight is distributed on the medial condyle.

PATHOLOGY

Fractures of the tibial plateau may involve one or both tibial condyles, or may involve the region between the condyles. It may be linear and incomplete, without displacement of fragments, or it may be complete, beginning anywhere along the plateau and terminating at the outer aspect of the condyle or tibial shaft, with a variable amount of lateral and downward displacement. The compression-type fracture may involve the anterior, posterior, or central aspect of the condyle, or of the entire condyle, with a variable degree of depression. With involvement of the lateral condyle the upper end of the fibula is frequently fractured and displaced, in which case the downward and lateral displacement of plateau fragments is more marked. The respective meniscus is probably always injured to some degree, and in some instances is fragmented and becomes interposed between the tibial fragments, or becomes a foreign body in the joint. With laceration of a collateral ligament the fracturing force of the opposite tibial plateau is lessened and, with separation of the adjacent femoral condyle and plateau, avulsion of the tibial spines or rupture of the cruciate ligaments occurs. Peroneal nerve injury is rare; none of our cases showed clinical evidence of nerve damage. Hemarthrosis is present in most cases and is often responsible for marked distention of the joint.

SYMPTOMS AND SIGNS

Pain over the site of injury is usually present but is rarely of severe nature. Disability is present in all cases but varies considerably in degree, being in general greater with medial condylar involvement than with involvement of the lateral condyle, due to the relation of the former to the line of weight bearing. Deformity of slight degree is occasionally noticed, with genu valgum present in depressed fractures of the lateral plateau. The knee is nearly always swollen and ecchymosis may be present. Joint fluid can be palpated and the patella is usually floating. There may be point tenderness over the site of bony or ligamentous injury with or without crepitation, and abnormal passive mobility can usually be demonstrated. With depression of one condyle there is abnormal lateral or medial mobility in varying amount. With depression of the posterior aspect of the plateau, there may be abnormal lateral mobility with the knee slightly flexed but not extended. With depression of the anterior aspect of the plateau, there may be hyperextension and slightly increased lateral mobility in extension. A presumptive diagnosis often can be made upon examination of the joint but final diagnosis depends upon x-ray studies, which should include right and left oblique views in addition to the anteroposterior and lateral aspects of the joint.

TREATMENT

Many different methods of treating plateau fractures have been suggested, but there has been no unanimity of opinion and, indeed, there have been numerous contradictions of principles of treatment proposed by various authors. In our series of cases there has been no standard of treatment, the manner in any individual case having been dependent upon the decision of the individual on

the service who at that time directed fracture treatment. The immediate treatment of practically all cases has been the application of a light pressure dressing to the knee with maintenance of the joint at absolute rest, and has been sufficient in most cases to resolve the swelling present. With marked joint distention, usually indicating a hemarthrosis, aspiration of the joint is done and may be repeated after twenty-four or forty-eight hours with recurrence of swelling.

Definitive treatment may be divided into several groups, each of which has its ardent advocates, in some instances almost to the complete exclusion of other methods of treatment. In principle, all methods seek to obtain a painless normal functioning knee joint.

Closed Reduction by Manipulation or by Various Devices.—Campbell, Cubbins, Jones, Cotton, Swett,[30] and Eliason have emphasized methods of closed reduction as being the procedure of choice in the treatment of these cases. Various leverage devices have been used to accomplish reduction, including Forrester's "redresseur," Caldwell's "nut-cracker," or carpenter clamps as described by Scudder. We believe, however, that satisfactory results can be obtained in most separation fractures by manual manipulation of the fragments and of drawing the leg to the opposite side to that of the fracture, maintaining it in this position by moulded splint, circular cast, or balanced suspension with or without traction until healing occurs. The collateral ligament, retaining its attachment to the fractured tibial condyle, tends to draw the fragments into position. This procedure is ineffective in reducing the comminuted depressed fragments in the central part of the tibial table which have no ligamentous or muscular attachments. In those cases of separation fracture with concomitant ligamentous tears, any of the aforementioned leverage devices may be required to effect reduction.

Early active motion is of utmost importance in the restoration of joint function. To this end balanced suspension provides protected motion with the leg in its normal weight-bearing axis. Motion with intact collateral ligaments will frequently effect replacement of the displaced fragments.

In some cases with marked separation or comminution and particularly in those cases with ligamentous tears, it is advisable, following reduction, to immobilize the joint in a cast to allow fixation of fragments by callus before protected mobilization is permitted. The period of protected mobilization is dependent upon progress of healing as indicated by periodic x-ray examinations and, as shown by Fig. 1, is optimally about two months. The patient is permitted to institute gradually increasing weight-bearing with crutches over a period of several weeks, finally bearing full weight, with or without a brace as severity of the injury indicates.

Forty-five per cent of our cases were treated with molded splints, and 17 per cent were treated with circular casing. Fifteen per cent of the cases were treated with balanced suspension with immediate active motion by means of Thomas splint and Pearson attachment. Early joint motion is believed to reduce the tendency to subsequent arthritic changes, and probably exerts few of the

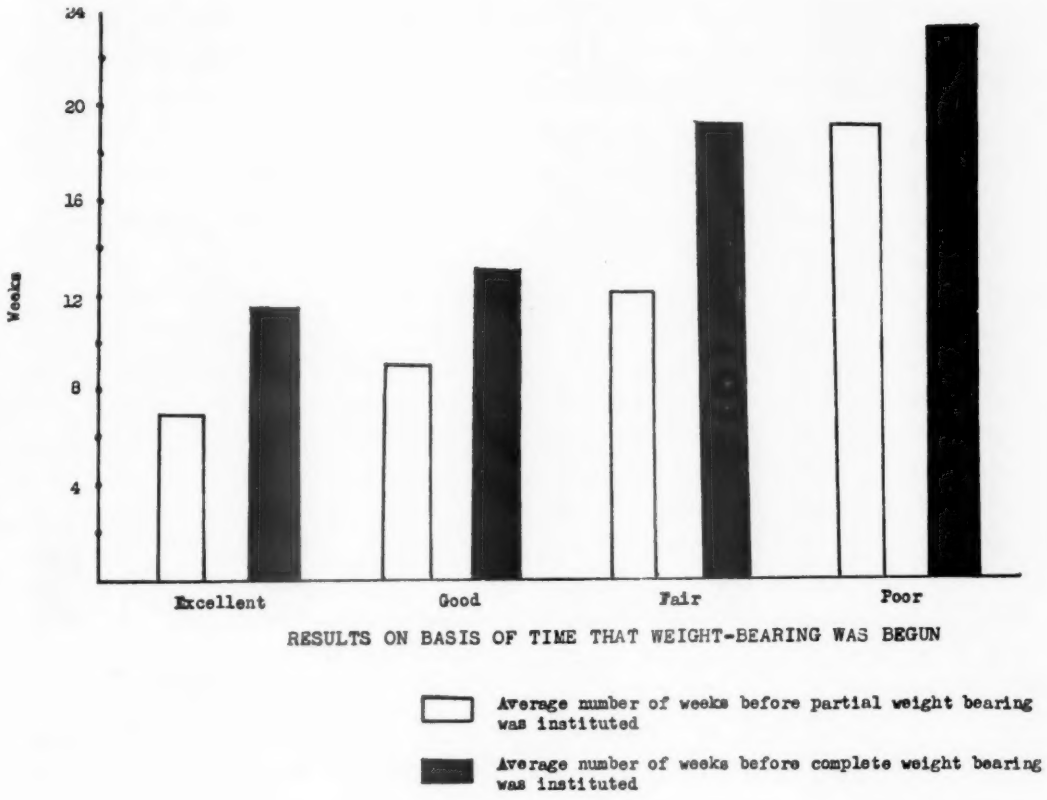
24
20
16
12
8
4
Weeks
Excellent
Good
Fair
Poor
RESULTS ON BASIS OF TIME THAT WEIGHT-BEARING WAS BEGUN
Average number of weeks before partial weight bearing was instituted
Average number of weeks before complete weight bearing was instituted

Fig. 1.

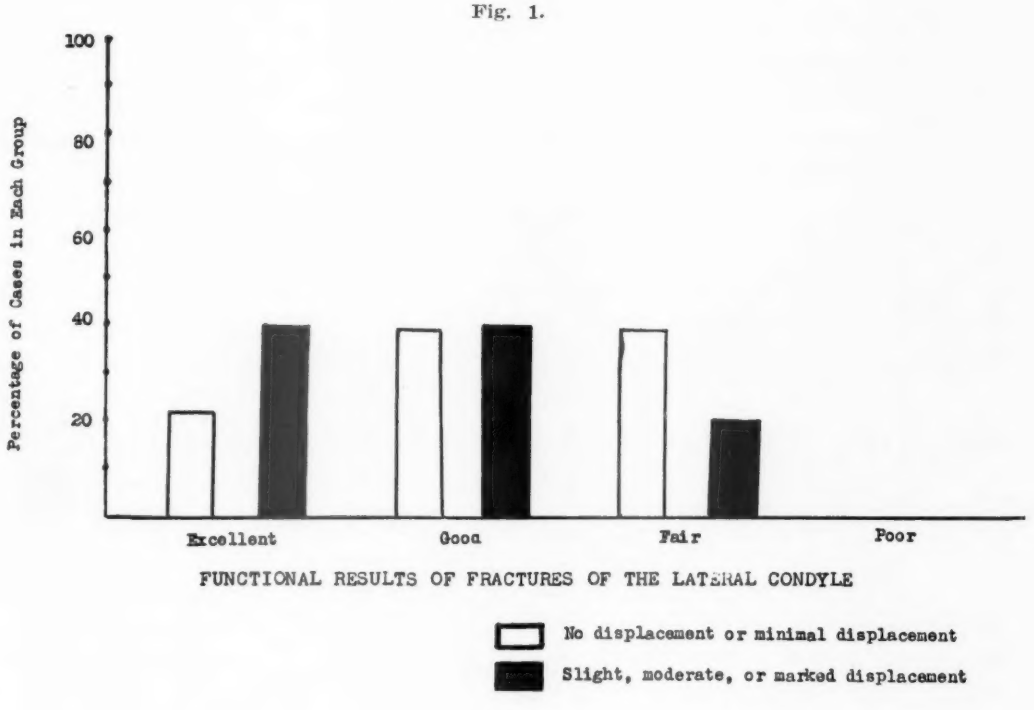
100
80
60
40
20
Percentage of Cases in Each Group
Excellent
Good
Fair
Poor
FUNCTIONAL RESULTS OF FRACTURES OF THE LATERAL CONDYLE
No displacement or minimal displacement
Slight, moderate, or marked displacement

Fig. 2.

damaging effects feared by Dyas and Goren. Suspension with traction was used in 7 per cent of the cases, while in 15 per cent a posterior molded splint was followed by balanced suspension with active motion.

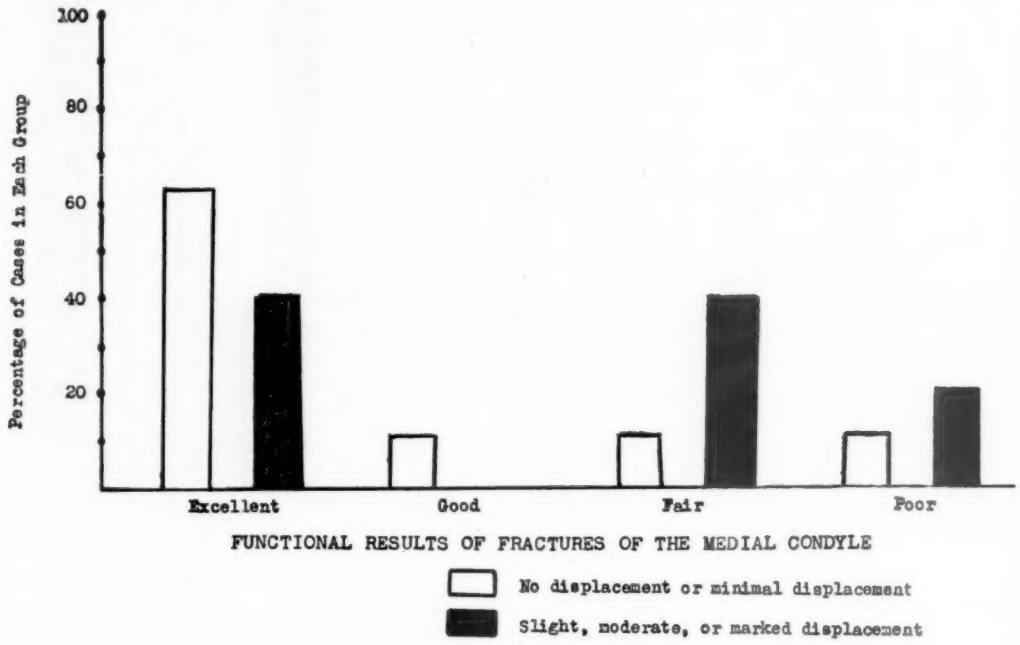

Fig. 3.

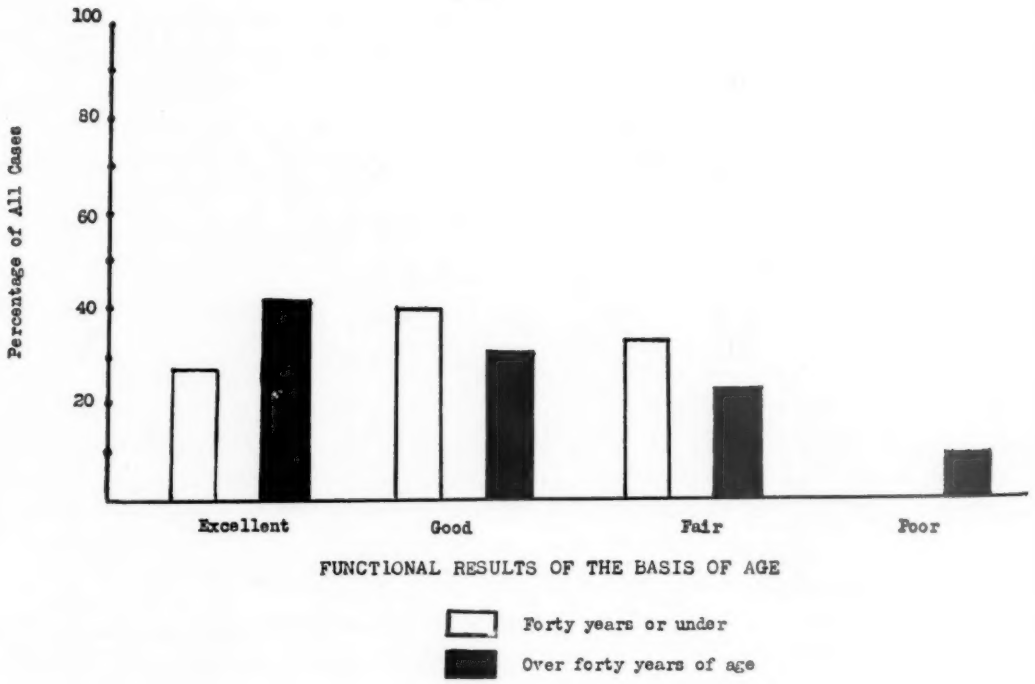

Fig. 4.

Unprotected Motion Without Weight-Bearing.—Linear fractures without separation or displacement were observed in 6 per cent of our cases; these were treated by simple immobilization upon pillows with the knee in 30° flexion until pain and swelling subsided. At this time increasing active movements of the joint were encouraged and weight-bearing begun in from three to six weeks.

Open Reduction.—Seven per cent of our cases were treated operatively. Cases with displacement of large fragments, especially entire condyles, are particularly suited for wiring or bolting. Difficulties encountered in the open reduction of the cancellous type bone of the tibial plateau should be emphasized. Greater fragmentation is a common result of attempts at manipulating or nailing the fractured portions of the condyle; best results are to be expected when dealing with fractures of an entire plateau. While difficulties of the procedure may be anticipated, markedly depressed, comminuted fractures which, as mentioned previously, cannot be satisfactorily reduced by closed manipulation, should be visualized and the fragments elevated from below by a dull flat periosteal elevator reducing the articulating surface. The underlying defect thereby produced may require the use of bone chips which may be taken from the corresponding femoral condyle, the tibia, or crest of the ilium. Postoperatively the joint should be immobilized with the knee in 15° flexion. Early protected mobilization is desirable and full weight-bearing instituted in from four to six months depending on x-ray evidence of healing.

PROGNOSIS

In all joint injuries, periarticular swelling with contraction of ligaments, tendon adhesions, and muscle atrophy occurs not only from the original trauma but from manipulations in reduction and long-standing immobilization. Muscle rehabilitation from the onset of injury is as important as early joint movement in reducing the deterring factors of function restoration.

Caldwell feels that disability and poor results are due to arthritic changes following articular damage and not to anatomic displacement alone. In the final analysis, end results are dependent on age, general condition of the individual, the joint status prior to injury, the effectiveness of reduction, and the use of early rehabilitation measures.

Of our series of 111 cases, a one-year follow-up was obtained in 43 per cent, while incomplete follow-up was observed in 27 per cent and no follow-up in 30 per cent. The oldest patient was 80 years, the youngest 13 years, 72 per cent being between 30 and 60 years of age. The effects of the amount of displacement in prognosis are indicated by Figs. 2 and 3. The manner in which age affected prognosis is indicated in Fig. 4. Best final results were observed in those patients in whom there was early joint mobilization. Better functional results occurred in those in which there was early weight-bearing, as indicated by Fig. 1.

SUMMARY

1. Fractures of the upper end of the tibia usually involving an articular surface ("tibial plateau fractures") result from one or both femoral condyles being forced by direct or indirect mechanism against the corresponding expanded cancellous tibial condyles, which may be crushed or split from the tibial shaft.

2. The relatively greater importance of fractures of the medial plateau, which bears the greater weight-bearing force, is emphasized.

3. There is an enhanced fracturing force when the opposite collateral ligament remains intact.

4. In our series of 111 cases, lateral plateau fractures were approximately twice as common as the other types.

5. Direct trauma by an automobile is by far the most common cause of plateau fractures.

6. The principle of closed reduction in the treatment of these fractures is based on the integrity of the collateral ligament on the side of the fractured plateau.

7. Open reduction with wiring or bolting of the fractured condyle is particularly suited to displacement of large fragments or with associated extensive ligamentous injury.

8. Poor results of these fractures are due to subsequent arthritic changes, and not to anatomic displacement per se. Insufficient functional rehabilitation may well contribute to poor success.

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NAIL DESIGN; AN IMPORTANT SAFETY FACTOR IN INTRAMEDULLARY NAILING

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AS A recent editorial by Cave (1949) indicated, the intramedullary nailing operation of Küntscher (1940) is being accepted in this country as a satisfactory method for the treatment of selected diaphyseal fractures of the femur. Since an integral part of this procedure involves driving a long metal nail through the entire length of the femur, from the trochanteric fossa to the condyles, one of the first questions raised by those observing such an operation for the first time has been: "But what about the danger of fat embolism?" It is the purpose of this paper to discuss some of the factors affecting the incidence of fat embolism in fracture patients treated with intramedullary nailing.

INTRODUCTION

Three conditions are essential for the production of fat embolism. These are: (1) the rupture of the fat cells; (2) the existence of venous channels by which the fat globules can reach the general circulation; and (3) an increase in the local tissue pressure to force the fat globules into the venous channels. The first two conditions are abundantly realized by the insertion of any intramedullary prosthesis with the consequent disruption of the bone marrow. The increase in local tissue pressure is the most essential and variable factor in the production of fat embolism, and it is this factor which is most affected by the design of the intramedullary nail.

Two types of intramedullary nails are readily available for use in fixing femur fractures, the hollow "cloverleaf" design extensively used in Europe, and the solid "diamond" design introduced by Street, Hansen, and Brewer, in 1947. Examination of nails of these two designs provoked the interesting speculation that the design or cross-sectional pattern of the nail should affect the production of fat embolism.

EXPERIMENTS

Because of the importance of the local tissue pressure factor in producing fat embolism, it was thought important to measure the pressures occurring in the intramedullary canal of one of the long bones during the insertion of an intramedullary nail. Measurements were made using hollow cloverleaf nails and solid diamond nails of similar caliber. They were driven into tibias removed from fresh amputation specimens with especial care to preserve the periosteum intact. The nails were inserted immediately in front of the tibial spines through a drill hole which pierced the tibial plate but did not penetrate the metaphysis. Pressures were measured by means of a capillary mercury

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manometer attached to a needle (No. 15) placed in the medullary cavity through a small hole in the cortex at the mid-point of the diaphysis. The nails were driven the full length of the shaft with blows of a hammer. The manometer was read continuously during insertion and the maximum readings recorded (Table I).

TABLE I. INTRAMEDULLARY PRESSURE ARISING DURING INSERTION OF INTRAMEDULLARY NAILS INTO TIBIAS

	HOLLOW CLOVERLEAF (MM. HG)	SOLID DIAMOND (MM. HG)
	58	170
	94	185
	70	100
	116	173
	75	180
	65	
Average	73	162

It should be noted that the pressure arising in the medullary cavity during the insertion of the solid diamond nail is about twice that arising during the insertion of the hollow cloverleaf nail.

In order to obtain further corroboration of these results, a series of similar experiments were performed using artificial "bones" composed of glass tubes 30 cm. by 1.5 cm. (the cortex and medullary canal of the diaphysis) and large corks which fitted snugly over the upper ends of the tubes (the cancellous metaphysis). The tubes were filled with a solution of agar (2 per cent)—"the fatty marrow." The distal ends of the tubes were closed with a rubber stopper with a hole for attachment to the capillary mercury manometer. Intramedullary nails of varying design were driven into these "bones" after boring a hole for insertion in the cork. The pressures were recorded in a manner entirely similar to the first experiment. The nails were of essentially similar caliber and consisted of a solid rod, a hollow tube, a V-shaped nail, the hollow cloverleaf nail, and the solid diamond nail. Ten determinations were made with each nail and the pressures recorded (Table II).

The pressure differential between nails of the solid and of the hollow designs is readily apparent.

TABLE II. PRESSURE OF INSERTION OF INTRAMEDULLARY NAILS INTO THE ARTIFICIAL "BONES"

	ROD (MM. HG)	TUBE (MM. HG)	V-SHAPE (MM. HG)	CLOVERLEAF (MM. HG)	DIAMOND (MM. HG)
	235	58	61	119	253
	180	95	40	105	290
	188	52	110	97	234
	260	62	80	144	346
	204	71	72	126	199
	365	70	60	80	224
	350	84	54	102	262
	284	78	64	104	210
	255	65	50	118	308
	216	80	68	115	286
Average	279	71	66	111	261

As a nail is inserted into the medullary cavity, it displaces a volume equal to its own bulk. This amount differs considerably with the design of the nail and represents the amount of fat and cellular debris which must escape from the medullary canal as the nail enters. Table III indicates the volume displacement of various types of nails and indicates the total amount of marrow substance displaced in fixing a femur of average size.

TABLE III. THE VOLUME DISPLACEMENT OF INTRAMEDULLARY NAILS OF SIMILAR CALIBER

	ROD (C.C.)	TUBE (C.C.)	V-SHAPE (C.C.)	CLOVERLEAF (C.C.)	DIAMOND (C.C.)
Volume displacement per 10 cm.	5.5	2.0	2.0	3.0	5.0
Volume displacement per 40 cm.*	22.0	8.0	8.0	12.0	20.0

*A nail 40 to 44 cm. long is needed to fix the average femur.

The smaller volume displacement of nails of the hollow design is easily demonstrable. What at first does not appear to be a significant difference is magnified to its proper proportions when the displacement of the entire nail is considered.

DISCUSSION

The long bones may be considered to be cylinders of cortical bone closed at each end with the cancellous bone of the metaphysis, and filled with the semiliquid bone marrow. The intramedullary nail entering the medullary cavity through the metaphysis acts as a piston to compress the marrow. If the nail is solid in design, no egress for the compressed marrow is provided. If the nail is hollow in design, the disrupted marrow flows out through the wound of insertion along the gutter of the nail. This difference in cross-sectional pattern is of fundamental importance in determining the intramedullary pressure during insertion (Fig. 1).

The clinical significance of the intramedullary pressure is already widely recognized. Küntscher (1940), Böhler (1944), and Moeys (1948) all ascribed the remarkably low incidence of clinical fat embolism following intramedullary fixation with nails of hollow design to the fact that the increase in the intramedullary pressure is minimal. Häbler (1949) advised periodic removal of the guide over which these nails are sometimes inserted to allow free flow of the escaping marrow. In one of his patients, this precaution was not observed. In fixing a fractured femur a second rod was forcibly inserted into a nail which had jammed. The resulting intramedullary pressure became so great that massive fat and air embolism occurred, with a fatal result. The function of the hollow type of nail as a "safety valve" to relieve the intramedullary pressure is further illustrated in the cases of infected fractures described by Böhler (1944). The hollow nail acted as a drain to relieve the tissue tension resulting from inflammation, effectively limiting the amount of sequestration. The experiments of Bisgard and Baker (1940) have demonstrated the effect of drainage of the medullary cavity in decreasing the number of fat emboli by preventing the increase in intramedullary pressure.

Unfortunately there exists no large series of cases treated with intramedullary nails of solid design which can be compared with the thousands of cases treated with the hollow nails to determine the incidence of fat embolism in relation to nail design. Rocher (1945), in France, and Street, Hansen, and Brewer (1947), in this country, are the only authors reporting cases treated with solid nails. Street and his co-workers appeared to be quite concerned about the dangers of fat embolism in their patients and advocated nailing only by open operation with lavage of the wound with ether to remove a portion of the fat displaced by the nail.

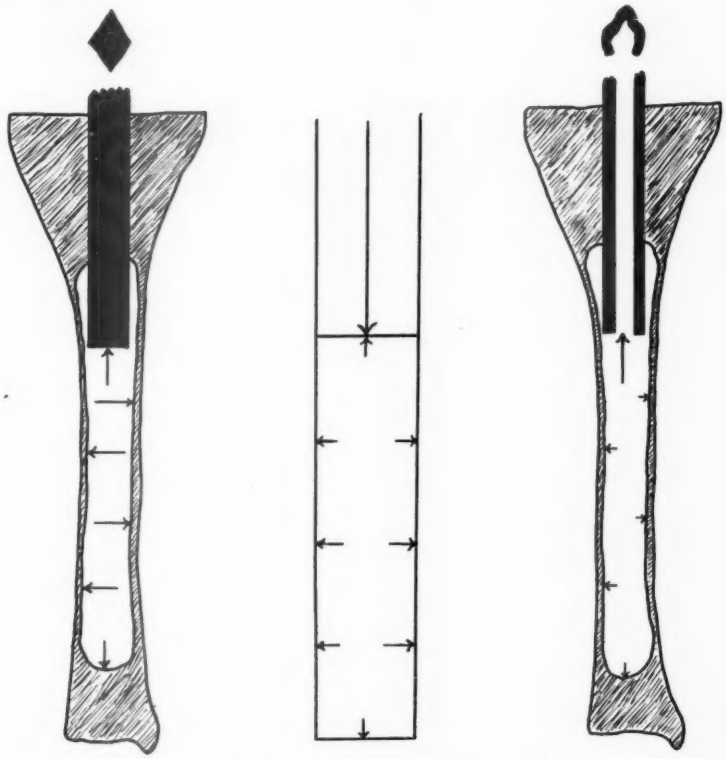

Fig. 1.—The diagram demonstrates the analogy between the solid nail and the piston in the cylinder. The hollow nail differs by offering free drainage of the medullary contents. This is an illustration of Pascal's Law that fluids transmit pressure equally in all directions.

Since the seriousness of fat embolism is directly proportional to the amount of fat entering the circulation, either directly through the venous sinuses of the marrow at the time of nailing or by venous absorption from the wound or fracture hematoma, the amount of fatty marrow displaced by the nail is important. This displaced fatty marrow represents potential fat emboli. Killian (1931), on the basis of careful post-mortem studies, concluded that as little as 12 to 20 Gm. of fat appearing in the lungs as emboli could produce serious symptoms and even death.

CONCLUSIONS

Important differences between intramedullary nails of a hollow and a solid design are immediately evident. Both the volume displacement and the intra-

medullary pressure during insertion are considerably greater with the solid designs. A solid diamond nail 40 cm. long displaces 20 c.c. of fatty marrow, and, during its insertion, the intramedullary pressure reaches 162 mm.Hg. A hollow cloverleaf nail of similar caliber 40 cm. long displaces 12 c.c. of fatty marrow, and during its insertion, the intramedullary pressure rises to 73 mm. Hg. The fat displaced by the hollow nail is provided with easy access to the wound of insertion, while the fat displaced by the solid nail finds this avenue of egress blocked. Since the danger of fat embolism is directly related to the amount of fat available for embolization, and to an increase in the local tissue pressure, it can be seen that the use of a hollow nail provides a greater margin of safety than does the solid nail because: (1) the volume displacement is smaller; (2) the drainage of the medullary canal is more effective; and (3) the intramedullary pressure arising during insertion is less.

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MALLEABLE LIGATURE CARRIER*

Designed for Use in the Surgery of Patent Ductus Arteriosus

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IN THE ligation or division of a patent ductus arteriosus a rupture of the ductus may occur. This is a serious complication and frequently may cause the death of the patient. The rupture is most likely to occur during the dissection posteriorly or when an attempt is made to pass a ligature around the ductus.

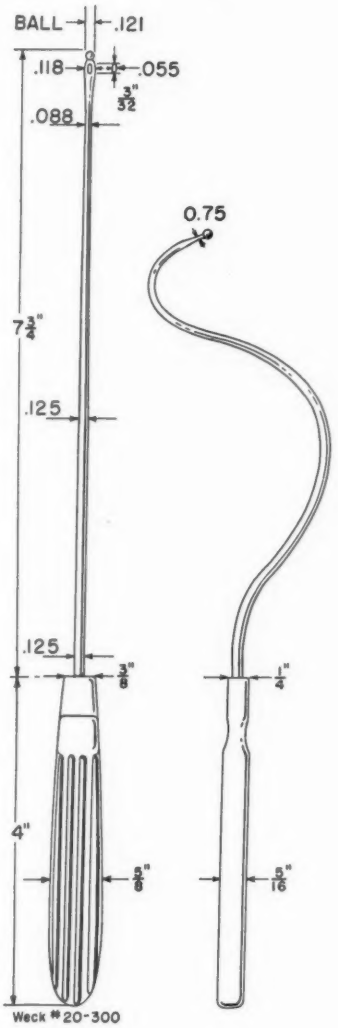

Fig. 1.—Drawings to scale of instrument: *A*, front view, full length; *B*, profile view, showing change in contour.

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*Manufactured by Edward Weck & Co., Inc., Brooklyn, N. Y.

Subsequent to the complete mobilization of a patent ductus arteriosus, encircling guy ligatures are a technical aid if a division is planned and a necessity if a ligation in continuity is performed. Frequently, however, there may be difficulty encircling the ductus with a ligature. The standard ligature carriers have not proved entirely satisfactory. Heretofore a kidney pedicle or "goose-neck" clamp has proved the most serviceable, but its size is a disadvantage. Furthermore, it is cumbersome to use and it is not suitable in all cases.

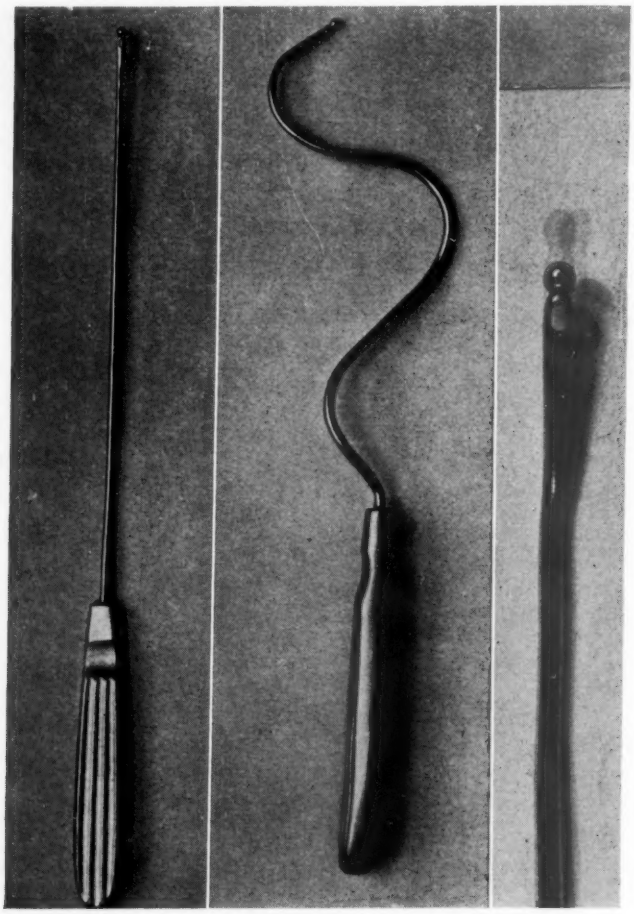

Fig. 2. Fig. 3. Fig. 4.

Fig. 2.—Full length photograph of instrument.
Fig. 3.—Malleability demonstrated by change in contour.
Fig. 4.—Close-up view of ball-point protector tip with eyelet.

To facilitate the application of encircling ligatures to a patent ductus arteriosus a malleable ligature carrier has been designed. Although designed for use in the surgery of patent ductus arteriosus, it may be employed expediently in ligation of the inferior vena cava or in other operations in which the ligation or division of large vascular channels is necessary. The features of this instrument are: (1) It has malleability, which permits an immediate change to the contour desired (Fig. 3). (2) The ball-point protector tip minimizes the possibility of perforation of the ductus (Fig. 4). (3) It is not cumbersome in size and it may be used with equal facility both in the child and in the adult.

Case Reports

OSTEOID OSTEOMA

A Case Report

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OSTEOID osteoma is now well established as a clinical and pathologic entity. Since Jaffe's classification of this lesion as a benign bone neoplasm in 1935 there have been many other cases reported. As he and others have pointed out, pain is the one constant clinical feature. Our objective in reporting an additional case is to emphasize that the pain may be referred to a site far removed from the true location of the lesion.

CASE REPORT

J. L. (Reg. No. 6263), a 21-year-old white man, a college student, was admitted to Veterans Administration Hospital, Vancouver, Washington, Aug. 18, 1948, complaining of pain, present since 1945, in the right elbow. The onset was gradual and was not associated with trauma. Past history and family history were noncontributory. He first noticed the pain particularly during periods of moderate activity, but it was not incapacitating. There was no history of swelling or redness of the elbow joint. As time passed, he discontinued those activities which produced the pain and was free from pain during the day. However, the pain later manifested itself in the elbow during the night and at times was severe enough to keep him awake for several hours.

The pain was almost constantly located on the medial surface of the elbow. It was described as boring in type and seemed deeply located, as if in the elbow joint itself. The distress became so disturbing to the patient that after a few months he consulted his physician, who, after taking roentgenograms of the elbow joint, told the patient that he had some muscular disturbance and prescribed heat treatments which gave no relief. During the subsequent two years he consulted several other physicians who took roentgenograms of the cervical vertebrae and shoulder joint. In the early part of 1948 he noted in addition to the elbow pain an occasional twinge in the right wrist following a vigorous handclasp. At the time of admission to this hospital he was rather vague about the pain in the forearm and related most of the symptoms to the right elbow.

Physical examination revealed a well-developed and well-nourished white man who showed no signs of acute or chronic general illness. The cervical vertebrae and right shoulder joint were entirely negative to physical examination. The right elbow joint presented a normal appearance with no swelling or muscular atrophy and there was a complete range of motion unattended by muscular spasm or pain. The right forearm appeared to be as well developed as the left, with good muscular power in the wrist and fingers. Passive supination was limited by 10 per cent as compared to the opposite extremity. Extreme supination produced slight pain located in the lower one-third of the forearm on the dorsal surface. On deep pressure here a marked tender area was found between the radius and ulna approximately 5 cm. above the wrist joint. By firm pressure the pain in the elbow joint could be reproduced.

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Fig. 1.

Fig. 2.

Fig. 3.

Figs. 1 and 2.—Anteroposterior and oblique views of lower end of radius showing thickening of cortical shaft with semicircular area of rarefaction.

Fig. 3.—Anteroposterior view of lower end of radius taken in the operating room following complete removal of the lesion and adjacent cortex.

Laboratory studies were within normal limits.

The roentgenograms (Figs. 1 and 2) revealed a sclerotic area of bone in the lower end of the radial shaft on its ulnar surface. The thickening resulted from periosteal new bone formation and its border was roughened. In the middle of this thickened cortical bone there was semicircular area of decreased density measuring 0.5 cm. in diameter and containing a central sclerotic focus. The lower border of this lesion extended to within 1 cm. of the distal articular margin of the radius. The medullary cavity appeared to be unaffected.

On September 8 the bone was exposed through a longitudinal incision in the lower one-third of the dorsal surface of the forearm where the lesion was recognizable as a roughened area on the dorso-ulnar border of the radius.

After carefully localizing the lesion with x-ray control, a block of bone including the entire lesion was removed (Fig. 3). During the removal the block fragmented, exposing a central nidus of soft, reddish tissue.

The hand and forearm were immobilized in a plaster of Paris cast for two weeks. On removal the wound was found to be completely healed.

Surgical Specimen.—The gross specimen consisted of three small irregular fragments of cortical bone covered on one surface by roughened periosteum. To the opposite surface of one there was attached a small nubbin of dark red-brown friable tissue.

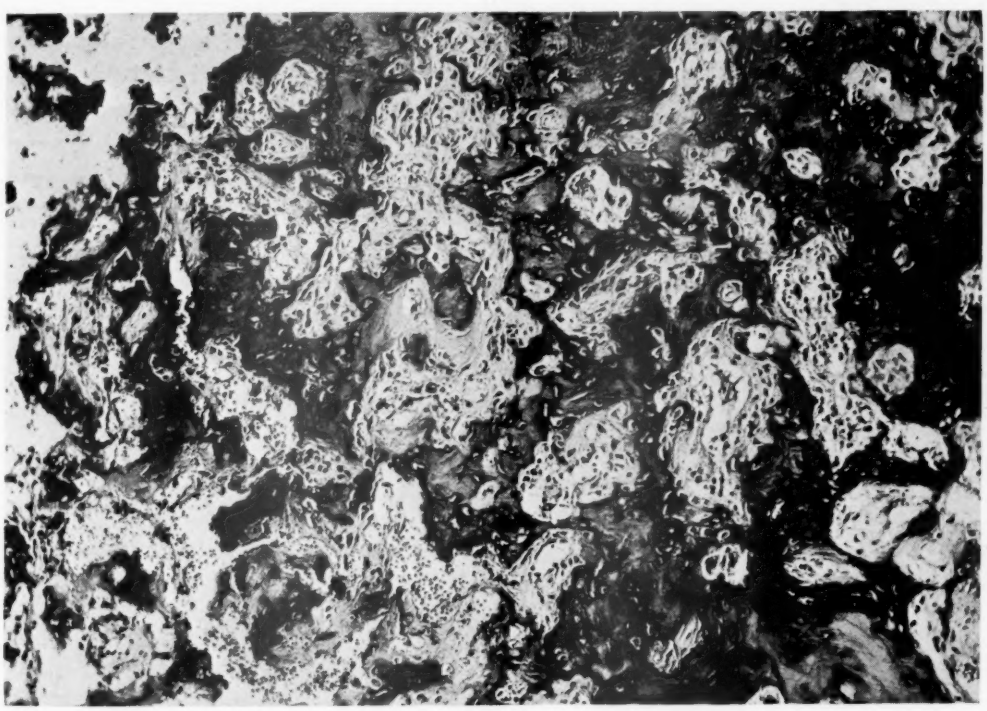

Fig. 4.—Photomicrograph, medium magnification, showing representative area of central nidus. Note irregular trabeculae of atypical calcified bone with bordering paler areas of osteoid and absence of inflammatory reaction in vascular stroma.

Microscopically (Fig. 4), this red-brown tissue was found to consist of irregular trabeculae of atypical calcified bone bordered in places by uneven zones of osteoid. The intervening loose fibrous tissue contained occasional vessels. The osteoblasts found lining the trabeculae appeared normal. The neoplasm was sharply delimited from the surrounding cortical bone. The adjacent cortex consisted of broadened trabeculae surrounded by loose fibrous connective tissue containing blood vessels. No evidence of inflammatory reaction was found in any of the numerous sections examined.

Postoperative Course.—On the morning following surgery the patient stated that he had spent the most comfortable night for some time and that the pain in the elbow joint had completely disappeared. He was discharged two weeks later completely free of pain.

This patient has been followed for five months and found symptom-free and able to carry on all normal activities without discomfort.

DISCUSSION

Although the pain, which is the cardinal symptom of osteoid osteoma, has received considerable attention from authors dealing with this subject, little mention of its radiation to distant sites can be found in the literature. In this case the pain was referred to the elbow joint. There was little to direct attention to the true site of the lesion, which was actually located in the lower end of the radius. We feel that this radiation of the characteristic pain is a very significant feature of the case, for it led to a delay in diagnosis until its true nature was appreciated.

SUMMARY

1. A case of osteoid osteoma in the shaft of the lower end of the radius with referred pain to the elbow joint has been reported.

2. It has been emphasized that the pain, which is a constant feature of this neoplasm, may be referred to a distant site, in this case to the proximal normal joint.

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EXTRAGENITAL CHORIOEPITHELIOMA IN THE MALE

A Case Report

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WHEN chorioepithelioma occurs in the male, the testes are usually considered first in a search for the primary lesion. Even though they may not show actual tumor, small cysts and scars have been found which were felt to represent primary lesions undergoing involution or healing.[1, 2, 3] There is disagreement as to how exacting a study of the testes is necessary. Some authors[4, 5] hold that a microscopic study of serial block sections is essential, while others[6] feel that a study of the testes by such a meticulous technique is unnecessary in every case of apparent extragenital origin, especially if there is an obvious primary lesion such as a teratoma of the mediastinum. Laipply and Shipley,[5] in 1945, applying the more strict criteria of serial block sections of the testes, found 8 acceptable cases, including 1 of their own. Since then there have been 3 other such cases[6, 7, 8] reported. Applying their more liberal view, Hirsch, Robbins, and Houghton[6] accepted 14 cases, including several rejected by other authors, and added 1 case of their own with a primary lesion in the mediastinum. The more recent report of Caes and Cragg[9] was most likely an extragenital chorioepithelioma, but it does not, as the authors stated, satisfy the strict criteria mentioned previously.

In the following case of a primary mediastinal teratoma with chorioepitheliomatous metastases in a male, the possibility of a genital origin was excluded by study of serial block sections of the testes.

CASE REPORT

M. B. (Reg. No. 6933), a 27-year-old white man, a garage mechanic, was admitted to the Veterans Administration Hospital, Vancouver, Wash., on Nov. 15, 1948, as a transfer from a private hospital where he had been admitted on November 7 complaining of abdominal pain of 2 weeks' duration. He had been well prior to this except for some abdominal discomfort and occasional cramps during the preceding summer. This patient was married and had 1 child about 1 year of age. On November 7 the pain became more severe and a diagnosis of acute appendicitis was made. At surgery the appendix appeared normal but a large amount of blood was found in the abdominal cavity. This was traced to a soft bleeding area 4 cm. in diameter on the under surface of the right lobe of the liver. A hard, nodular mass could also be felt within the liver. A biopsy from the edge of the bleeding area was taken. Sutures and gauze packing were used to control the bleeding and the abdomen was closed. He received 4 pints of blood during the next few days. The biopsy revealed chorioepithelioma.

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When admitted to the Veterans Administration Hospital, he was pale and complained of abdominal pain. Blood pressure was 124/76, pulse 100, and temperature 99.4° Fahrenheit. The abdomen was distended and a gauze drain was present in the right flank. The right side of the abdomen was dull to percussion and the left side tympanitic. There was decreased motion of the right chest with dullness to percussion and absence of breath sounds up to the third interspace. Both testicles were normal, as were the breasts.

The red blood cell count was 2,500,000, hemoglobin 45 per cent (7 Gm.), and white blood cell count 12,350, with a normal differential. Blood protein was 5.88 Gm. with albumin 2.7, and globulin 3.18. Prothrombin time was 40 per cent of normal. A Friedman test was positive.

Roentgenogram of the chest (Fig. 1) showed a huge nodular mass of soft tissue occupying the anteroinferior two-thirds of the right chest. This was believed to be an intrathoracic neoplasm. With this -xray finding and the apparently normal testicles, the possibility of a primary mediastinal neoplasm was seriously considered.

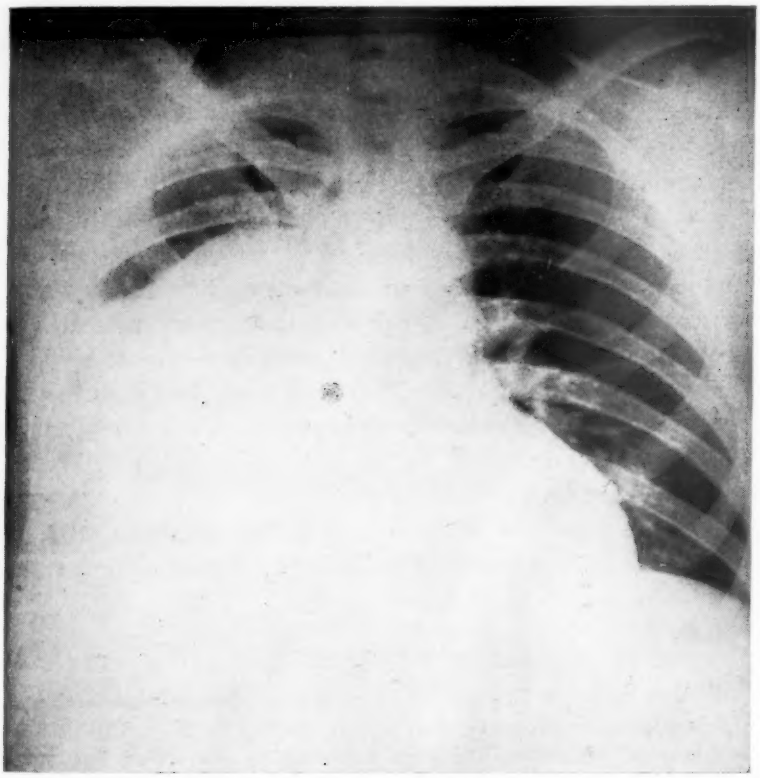


Fig. 1.—Posterior-anterior view showing large mass occupying inferior two-thirds of right chest.

He was placed on 50,000 units of penicillin every 3 hours and given 2,000 c.c. of whole blood during the next 2 days.

Twenty-four hour urine specimens were collected for determining amounts of gonadotropin excreted. Assays performed at the University of Oregon Medical School indicated that large amounts of chorionic gonadotropin were being excreted. By comparing with the International Standard preparation it was found that the amount excreted approximated 2,000,000 units per 24 hours.

On November 17 the red blood cell count was 2,800,000, hemoglobin 45 per cent, and white blood cell count 11,500. Small amounts of blood continued to ooze from the wound and the right side of the abdomen became more distended. The liver was palpable about 10 cm. below the costal margin.

The patient's dyspnea increased so that he was placed on oxygen and given another 1,000 c.c. of blood. On the fourth hospital day he began to vomit and became more distended. This was partially relieved with a Miller-Abbott tube. Because of the evidence of increased bleeding the abdomen was again opened on November 23 and about 3,000 c.c. of clotted and fluid blood removed. The liver was found to be enormous and to consist mainly of hemorrhagic masses, the largest measuring about 12 cm. in diameter. Bleeding was fairly well controlled with Oxycel and Gelfoam and the abdomen closed after a biopsy was taken. This also showed chorioepithelioma.

The postoperative course was progressively worse and the patient died Nov. 26, 1948.

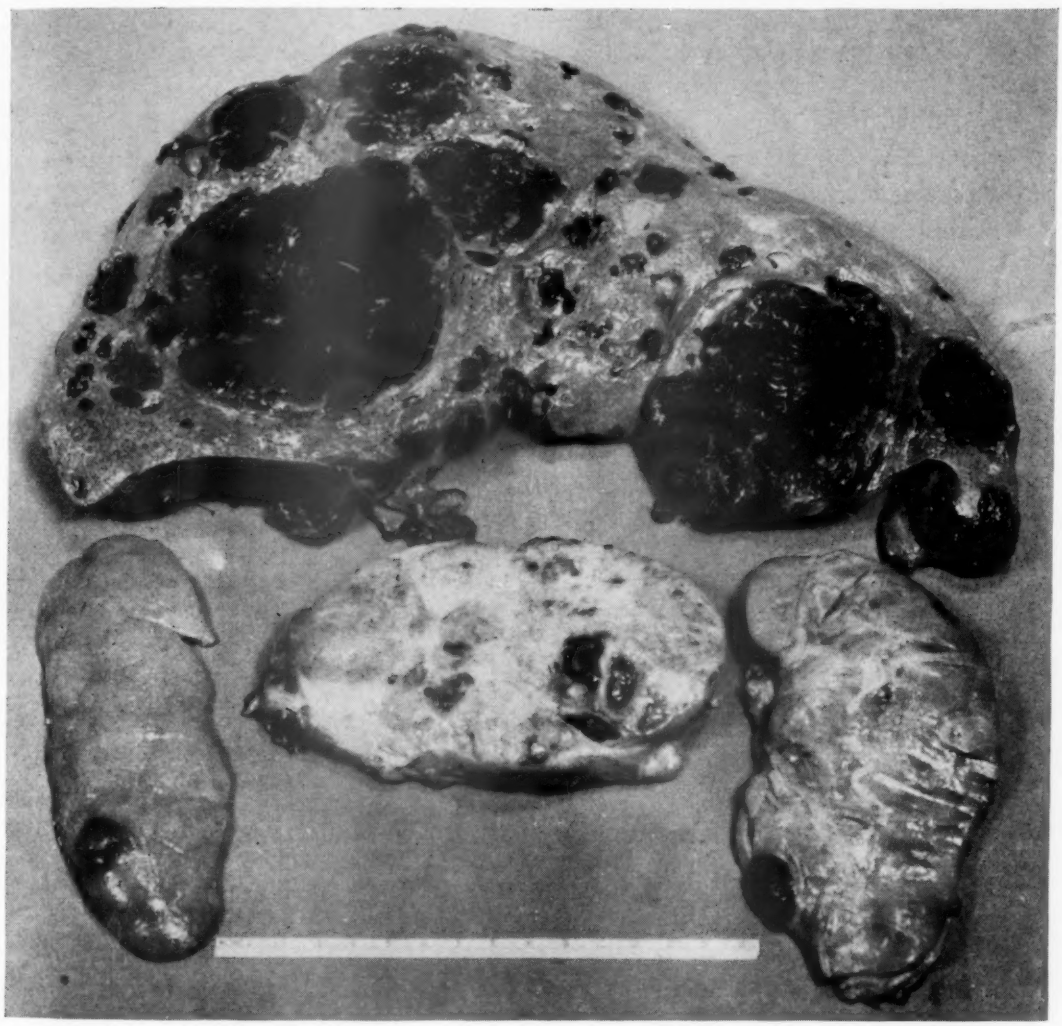


Fig. 2.—Gross autopsy specimens. Note the varied appearance seen in cross section of thoracic teratocarcinoma (center), and hemorrhagic character of metastases in liver section (above) and kidneys.

AUTOPSY

The significant final anatomic diagnoses were as follows: (1) primary teratocarcinoma of the right anterior mediastinum; (2) chorioepitheliomatous metastases to lungs, liver, pancreas, and kidneys; (3) atrophy of seminiferous

tubules and hyperplasia of the interstitial cells of the testes; (4) hyperplasia of the ductal epithelium of the breasts; and (5) atelectasis of the right lower lobe of the lung.

The body was that of a well-developed and well-nourished young white man, and showed no external abnormalities except for the evidence of the previous abdominal surgery. The breasts were normal to palpation, as were the testes. Approximately 300 c.c. of thin, dark red-brown fluid were found in the peritoneal cavity. An oval, circumscribed, hard, light gray mass weighing 660 Gm. and measuring 15.0 by 13.0 by 7.5 cm. in its maximum diameters was found occupying the anteroinferior portion of the right thoracic cavity. The mass was beneath the parietal pleura and was densely adherent to the anterior mediastinum. The right lower lobe was compressed posteriorly by the tumor to which it was attached by fibrous adhesions. The tumor cut with resistance and the cut surface presented a variegated appearance with large and small smooth-walled cystic spaces separated by dense strands of gray-white, fibrous-appearing material (Fig. 2). Soft, dark red areas having a hemorrhagic appearance were scattered throughout. There was no evidence of hair, teeth, or other organoid structures.

The liver weighed 6,640 Gm. and was studded on the external and cut surfaces with a large number of hemorrhagic friable nodules varying in diameter from 0.5 to 9.0 cm. (Fig. 2). On the inferior surface of the right lobe several of these masses had ragged surfaces and were covered with oxycel gauze which was sutured to the capsule. A 1.0 cm. hemorrhagic nodule was found in the left upper lobe of the lung, another 1 in the pancreas and 2 in the right kidney (Fig. 2).

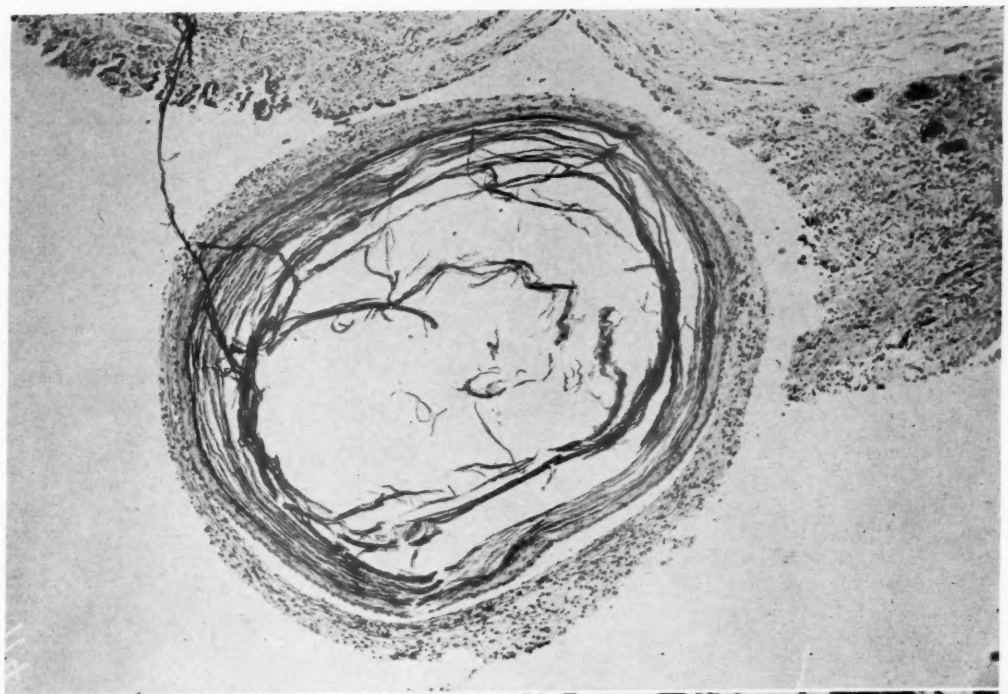
Both testicles were removed and divided in their long axis. Each half was then cut into blocks approximately 2.0 mm. in thickness and no evidence of neoplasm or scarring was found.

Gross examination of the brain revealed no abnormalities. The pituitary was normal in size and appearance.

MICROSCOPIC EXAMINATION

Microsections of the thoracic tumor showed a varied structure. There were numerous cysts. Some, lined by keratinizing stratified squamous epithelium, were filled with keratohyaline debris (Fig. 3). Others lined with tall columnar ciliated cells contained a pale mucoid material. Still other irregular spaces were bordered by low cuboidal epithelium. The stroma consisted of relatively acellular fibrous connective tissue within which there were islands of loose pale myxomatous tissue and cartilage-like material. There were short strands of what appeared to be myelinated nerve. Large fields were composed of irregular, endothelial-lined, blood vascular spaces separated by thin septa. The areas of hemorrhage and necrosis noted grossly were bordered by neoplastic cells having basophilic cytoplasm and large nuclei with prominent nucleoli and clumped chromatin (Fig. 4). These resembled Langhan's cells.

Fig. 3.



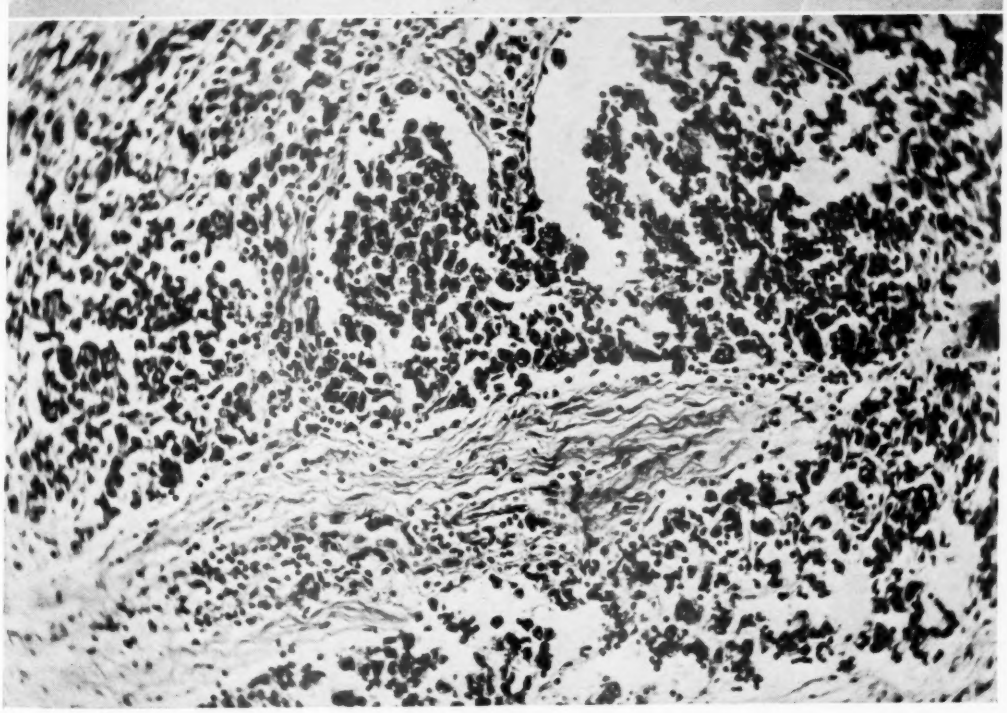


Fig. 4.

Fig. 3.—Cyst from thoracic neoplasm lined by keratinizing stratified squamous epithelium. Cuboidal epithelium may be seen above (×100).

Fig. 4.—High-power view of area of thoracic neoplasm showing malignant epithelial cells resembling Langhan's cells (×200).

Fig. 5.

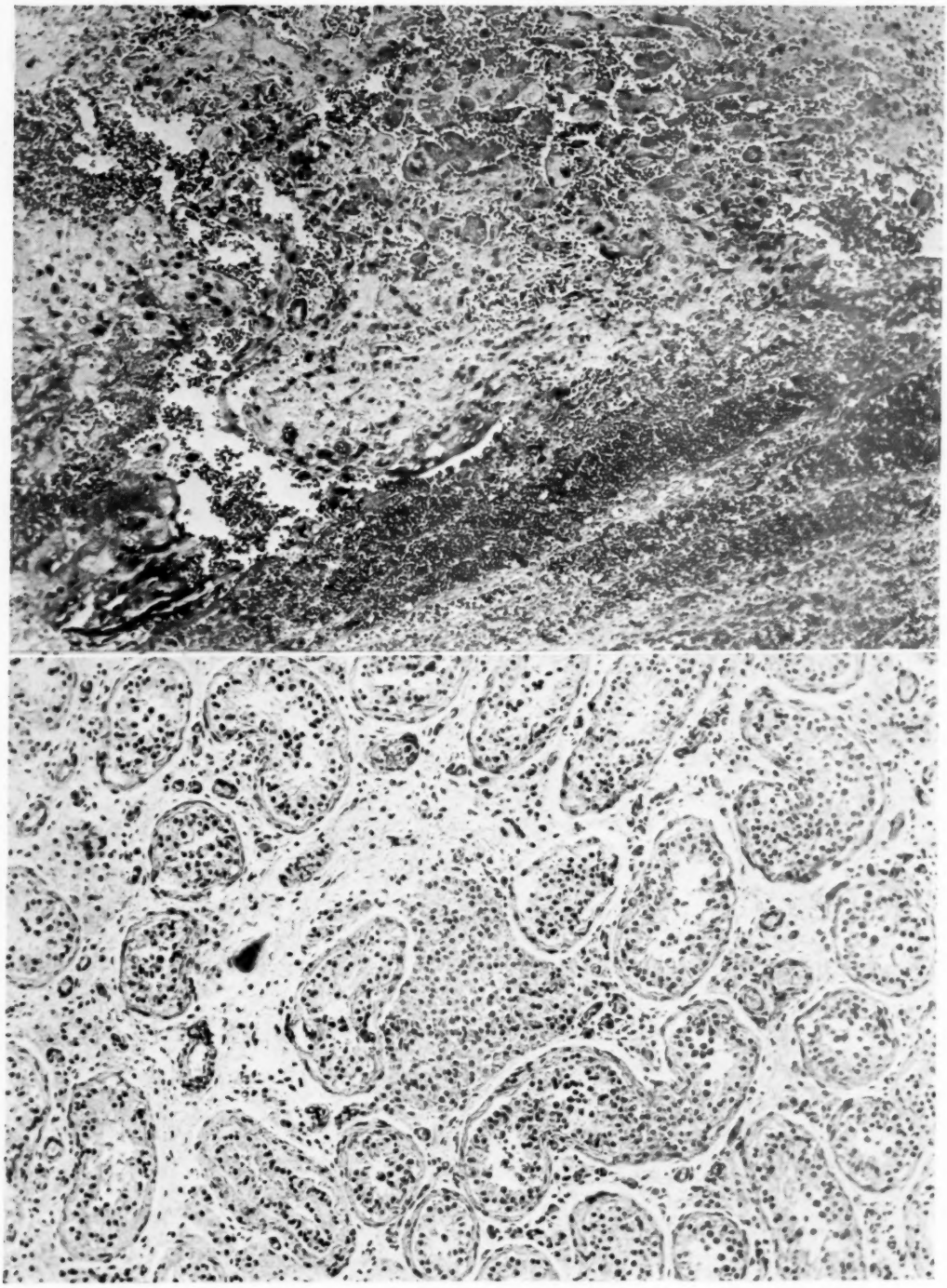


Fig. 6.

Fig. 5.—Border of liver metastasis. Hemorrhagic area below with invaded liver parenchyma (×100).

Fig. 6.—Representative area of testis. Note degenerative changes in seminiferous tubules and marked hyperplasia of interstitial cells.

The metastatic nodules in the liver, lung, pancreas, and kidney were made up of central areas of hemorrhage and necrosis surrounded by neoplastic cells (Fig. 5). In addition to those of the Langhan's type there were other syncytial cell masses having abundant eosinophilic cytoplasm and irregular hyperchromatic nuclei.

Study of at least 2 sections from different levels of each of 21 blocks comprising the entire right testicle and 16 blocks from the left testicle showed no evidence of neoplasm or scarring. There was an absence of spermatogenesis with degeneration of the tubular epithelium and hyalinization about the periphery of the tubules. Hyperplasia of the interstitial cells was pronounced (Fig. 6).

Microsections of the breasts revealed a proliferation of the ductal epithelium and a loose periductal connective tissue containing an occasional lymphocyte.

The anterior lobe of the pituitary contained an increased number of eosinophilic cells resembling the so-called "pregnancy cells" described by Erdheim and Stumme.[10]

COMMENT

The clinical diagnosis of chorioepithelioma in this case was made after biopsy of a hemorrhagic liver metastasis at the time of abdominal exploration for an "acute abdomen." The diagnosis was confirmed by assays of urine with recovery of large amounts of chorionic gonadotropin. The possibility of an extragenital primary lesion was suggested by the finding of palpably normal testes and a large intrathoracic mass demonstrated on x-ray examination of the chest. Review of a chest roentgenogram taken at the time of induction into the Navy in 1942 showed no evidence of this tumor. There is the possibility that had a chest roentgenogram been taken in this interval it might have revealed this tumor, which could have been removed before metastasis had taken place. In this case, as in others, there were no symptoms until those produced by the metastatic lesion.

The autopsy findings showed the thoracic mass to be a teratocarcinoma composed of elements of all 3 germ layers with undifferentiated neoplastic cells resembling the Langhan's cells of the placenta. The metastases were chorioepitheliomatous in nature. Serial block study of both testes excluded the possibility of any primary lesion in these organs.

Chorioepitheliomas arising outside of the genital organs have usually been explained as being derived from germinal rests[11] or from malignant transformations or unilateral development of a teratoma.[8] In the case reported herein the latter explanation would seem to hold in that origin in a well-defined mediastinal teratoma was demonstrated with recognizable teratomatous elements remaining in the primary tumor. Erdmann, Brown, and Shaw[4] stated that the genesis of teratomas is speculative. Schlumberger,[12] in a study of the origin and development of teratoma of the anterior mediastinum from the standpoint of embryology, reviewed the various hypothesis which have been offered and concluded that these tumors arise in tissue dislocations in the anlage of the

thymus and would be more properly designated as teratoma of the thymus. According to Willis,[13] mediastinal teratomas almost always arise from the anterior mediastinum and are usually of the benign cystic variety but when malignant are most often adenocarcinomatous or chorioepitheliomatous.

SUMMARY

1. A case of extragenital chorioepithelioma in a male is reported; the primary site was a teratocarcinoma of the anterior mediastinum. Origin in the testes was excluded by a careful study of serial block sections.

2. There was microscopic evidence of gynecomastia, atrophy of seminiferous tubules, and hyperplasia of the interstitial cells of the testes.

3. The clinical diagnosis was made by biopsy of a liver metastasis and urine assays for chorionic gonadotropins.

4. This is believed to be the twelfth case of proved extragenital chorioepithelioma reported in a male.

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THE WATERHOUSE-FRIDERICHSEN SYNDROME IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE ABDOMINAL CRISES

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ACUTE bilateral hemorrhage of the adrenals, complicating a fulminating sepsis, has been reported, principally in journals of pediatrics, pathology, or internal medicine. The accompanying syndrome, named after Waterhouse[1] and Friderichsen,[2] who were among the early authors to discuss it, is ordinarily a result of meningococcus septicemia, and in 70 to 90 per cent of the reported cases has occurred in children under 2 years of age.

The characteristic clinical picture is one of sudden profound collapse following prodromal symptoms typical of infectious disease. The patient becomes cyanotic and, within a few hours, exhibits multiple petechial hemorrhages; the extremities become cold; however, the body temperature may range up to 108° F. The blood pressure drops to shock levels, with attendant mental changes, and an anuria followed by oliguria.[3] The patient's general condition deteriorates rapidly, and may exhibit any of the common terminal signs of death-in-shock, usually within twenty-four to forty-eight hours, even when the correct diagnosis is made and appropriate treatment instituted.

The recent literature has tended to deal with the unusual cases: those occurring in adults, those associated with nonmeningococcic infections, and those, now numbering about twelve, in which the patients have survived with the aid of large doses of adrenal cortical extract together with the antibiotics.

The Waterhouse-Friderichsen syndrome is not ordinarily a surgical disease, and consequently the surgeon seldom encounters it. A search of the available literature reveals only one previous discussion of the syndrome from a surgical aspect.[4] Our recent experience has prompted us to report the following case illustrating how adrenal hemorrhage may pose a difficult problem in surgical differential diagnosis.

CASE REPORT

M. W., a white widow 53 years of age, entered the University Hospital at 8:00 P.M., Feb. 10, 1949, complaining of severe abdominal pain of six hours' duration. She had been bowling in the morning and had been quite well up until 2:00 P.M., at which time she began to feel "cold and shaky." After a few minutes she was seized with severe hypogastric and left epigastric pain which radiated to her back and down her thighs. The pain persisted even after her family physician had given her 3 mg. of Dilaudid at 5:30 P.M. She was moderately nauseated and vomited a small amount during this period.

Her past history and system review revealed that during the month preceding admission she had noticed a scanty, painless, blood-tinged vaginal discharge which she interpreted as menopausal.

On physical examination she was found to be moderately obese and in acute distress, rolling and threshing about in bed. Blood pressure was 70/50, pulse 140 and regular, re-

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spirations 36, and temperature 104° F. The pupils were constricted but were symmetrical, the neck was not rigid and was free of pain on both active and passive movement. The heart and lungs were normal.

The abdomen was distended; it was doughy in consistency and generally tender, particularly in the upper left and lower right quadrants. There was diffuse rebound tenderness, the bowel sounds were greatly diminished, and respiratory motion decreased. No masses were felt on abdominal, pelvic, or rectal examination. The pelvic structures were not tender but there was a small amount of blood-tinged vaginal discharge. The remainder of the physical examination was not remarkable except for a peculiar dusky cyanosis of the face and extremities.

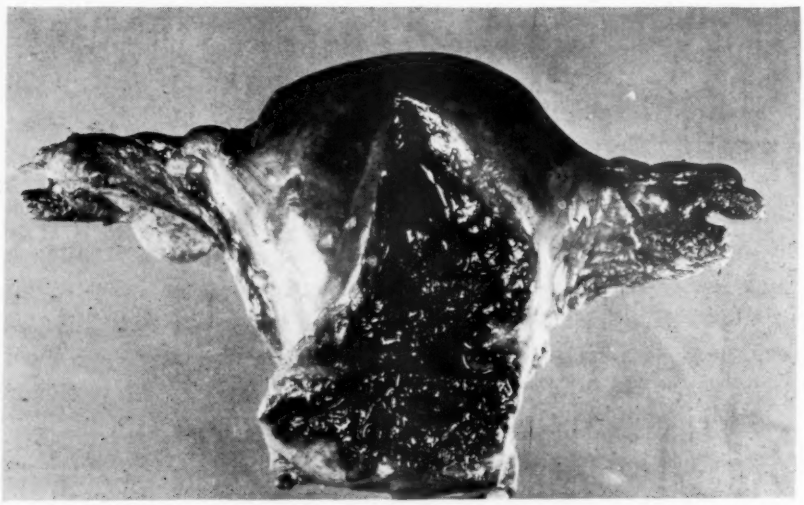

Fig. 1.—The uterus, showing the sanguinopurulent exudate in the endometrial cavity.

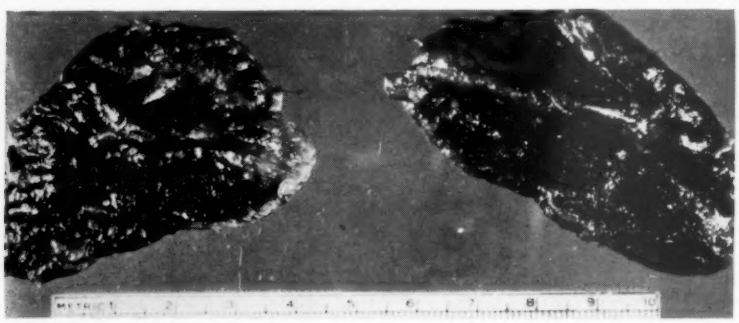

Fig. 2.—The adrenals, showing the tense, enlarged hemorrhagic appearance.

The admission laboratory findings were as follows: red blood cells 4.3 million, total white blood cells 5,600; 46 per cent segmented neutrophils, 20 per cent nonsegmented neutrophils, 30 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophils. Urinalysis was not abnormal. Blood amylase was 70 Somogyi units. The CO_2 combining power was 26 volumes per cent, the blood urea nitrogen 35 5, the blood sugar 78.0, and the blood chlorides 511.5. Roentgenograms of the chest and abdomen, as well as the electrocardiogram, demonstrated no abnormalities.

In view of the shock, together with the absence of localizing signs of surgical disease, it was decided that restorative and supportive measures were indicated, rather than immediate laparotomy. Accordingly, after a blood culture had been taken, she was placed on

Fig. 3.

Fig. 4.

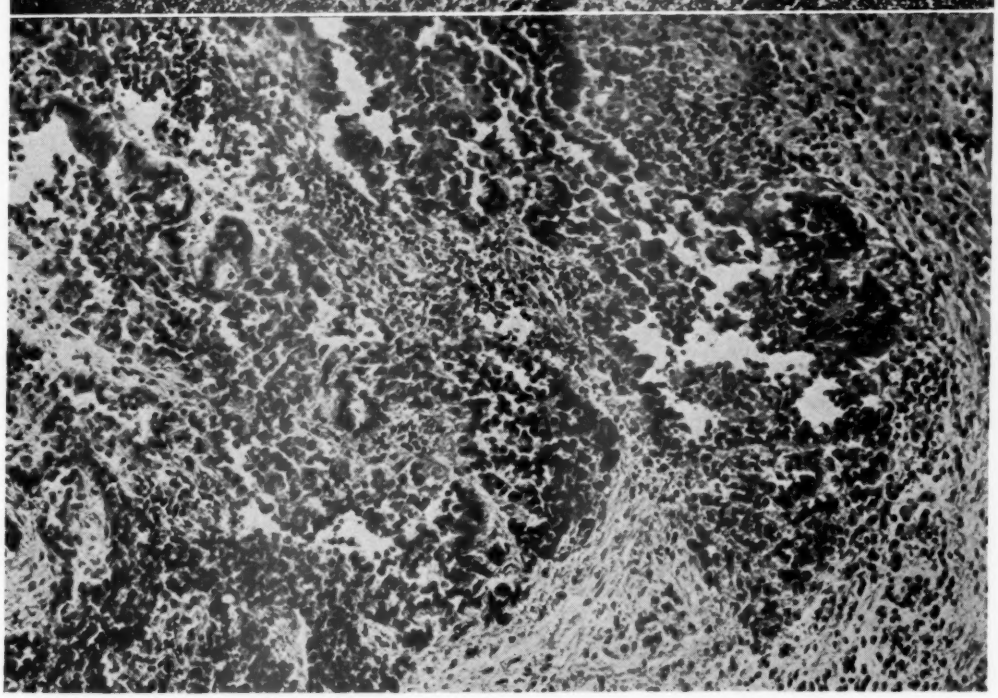

Fig. 3.—Photomicrograph of a section of adrenal demonstrating the massive hemorrhage.
Fig. 4.—Photomicrograph of the endometrial carcinoma with the secondary inflammatory exudate.

large doses of penicillin and streptomycin, given oxygen by intranasal catheter, and given intravenous fluid therapy, including whole blood. Wangensteen suction through a Levine tube removed a large quantity of gas and 200 c.c. of greenish black fluid, relieving some of the distention.

The temperature dropped briefly to 102.4° F. but climbed again to 106° F. by 8:00 A.M. of the morning following admission; by the same time the blood pressure had dropped to 44/20. There were no important changes in her other physical findings and she remained conscious but not alert, continuing to suffer great pain. Although the total extent of her condition remained unrecognized, she received an initial dose of 10 c.c. of adrenal cortical extract. An internist's consultation added nothing to diagnosis or therapy.

During the latter part of the morning her cyanosis increased and the gastric drainage became dark brown and microscopically was found loaded with red blood cells. She failed, however, to improve to the point where this latter finding could be further investigated by even the most conservative means. At 1:35 P.M., approximately 17 hours after admission, she expired.

At autopsy minimal clear exudates were found in the peritoneum and pericardium, but not in the pleural spaces. The heart, lungs, great thoracic vessels, liver, spleen, pancreas, kidneys, and small and large bowels were normal. The stomach contained a small amount of old blood without demonstrable origin, and the gall bladder contained several small cholesterol stones. The ovaries were atrophic and the tubes were not unusual, but the uterus was enlarged, flabby, and congested, with a patulous, ulcerated cervix. The endometrium was jagged and the uterine cavity contained some foul, dark red, partly clotted, sanguinopurulent material (Fig. 1). Both adrenals were enlarged, tense, and hemorrhagic (Fig. 2).

Microscopic examination of the necropsy specimens revealed destruction of the normal architecture of the adrenals by massive hemorrhage (Fig. 3), and a primary carcinoma of the uterus with secondary infection (Fig. 4). The final diagnosis was bilateral massive adrenal hemorrhage, brought on by overwhelming septicemia which was produced originally by severe infection of a poorly differentiated endometrial carcinoma. The organism implicated by the blood culture was an anaerobic streptococcus.

DISCUSSION

The case reported is of an entity not previously discussed in American surgical literature, so far as can be determined. Although the Waterhouse-Friderichsen syndrome is not as rare as was once thought, its sudden occurrence as a severe abdominal crisis in an adult with no prodromal symptoms is highly unusual and becomes a matter of interest to the surgeon. This case serves to emphasize the inadvisability of exploring a profoundly depressed patient in whom one cannot determine either the type or the location of a pathologic process. It is felt that adherence to sound diagnostic principles is the best insurance against ill-advised laparotomy in cases presenting this syndrome. Reports of recovery are still so rare that there is no established treatment. Nevertheless, it appears evident that large doses of adrenal cortical extract, the antibiotics, and fluid therapy in accordance with the clinical and laboratory findings are advisable.

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MIKULICZ'S DISEASE OF PAROTID GLANDS

Report of a Case

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WE HAVE encountered an unusually large bilateral tumor of the parotid gland. Large bilateral tumors of the parotid gland have received scant attention in the literature. The management of this case presented a serious problem. The clinical setting of the tumor suggested its benign nature, but the progressive facial asymmetry was of major concern to the patient.

CASE REPORT

A 59-year-old married white carpenter was examined on January 12, 1949. In 1941 he first noted onset of enlargement of both parotid glands, unassociated with trauma, pain, fever, or facial nerve weakness. This swelling was progressive and asymptomatic over the eight years. There was no intercurrent illness, and no specific treatment for these tumors. Past history was not contributory. The patient sought medical advice because of the cosmetic deformity (see Fig. 1).

Pertinent physical findings were confined to the head and neck where bilateral, oval, multinodular homogeneously firm and painless tumors were noted over the parotid areas. These masses measured 10 by 7 cm. and 11 by 8 cm. on the right and left sides, respectively. The overlying skin was erythematous and movable. The lesions were fixed to the underlying tissues. Both auricles were displaced posteriorly. There was no encroachment on the pharynx, and no cervical nodes were palpable. The tumors extended from the level of the supraorbital ridge down to the carotid bifurcation and from the mastoid process to the zygoma. Lacrimal, submaxillary, and sublingual glands were not palpable.

Complete blood and urine examinations were normal. Complement fixation and Mazzini tests were negative. A chest film was also normal. Aspiration biopsy of the right parotid gland was interpreted as containing parotid tissue and lymphocytes, but was insufficient for diagnosis. A sialogram (Figs. 3 and 4) of the left parotid revealed excellent filling of the ductal system with widespread displacement of the ducts about an extensive soft-parts mass with some puddling of the opaque medium. On the basis of these findings, a provisional diagnosis of bilateral adenolymphoma of the parotid gland was made, and surgical excision was recommended.

At operation on Jan. 18, 1949, the right facial nerve was identified at its point of exit from the stylohyoid foramen and the entire parotid exposed. Tissue removed from the gland and examined by frozen section was reported as benign tumor. The entire parotid was resected, saving the main trunk and peripheral branches of the facial nerve. The right subdigastric node was also removed at this time and was reported to be normal lymphoid tissue. Histopathologic examination (Figs. 5 and 6) of the excised gland showed chronic inflammation, consistent with Mikulicz's disease.† The postoperative course was uncomplicated except for complete right facial nerve palsy from which the patient recovered

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†Dr. Fred Stewart, Memorial Hospital, New York, N. Y., and Dr. Shields Warren, New England Deaconess Hospital, Boston, Mass., reviewed these slides and concurred in this opinion.

Fig. 1. Fig. 2.

Fig. 1.—Preoperative photograph demonstrating bilateral parotid tumors.

Fig. 2.—Postoperative photograph following total resection of both parotid glands with preservation of facial nerves and absence of facial palsy.

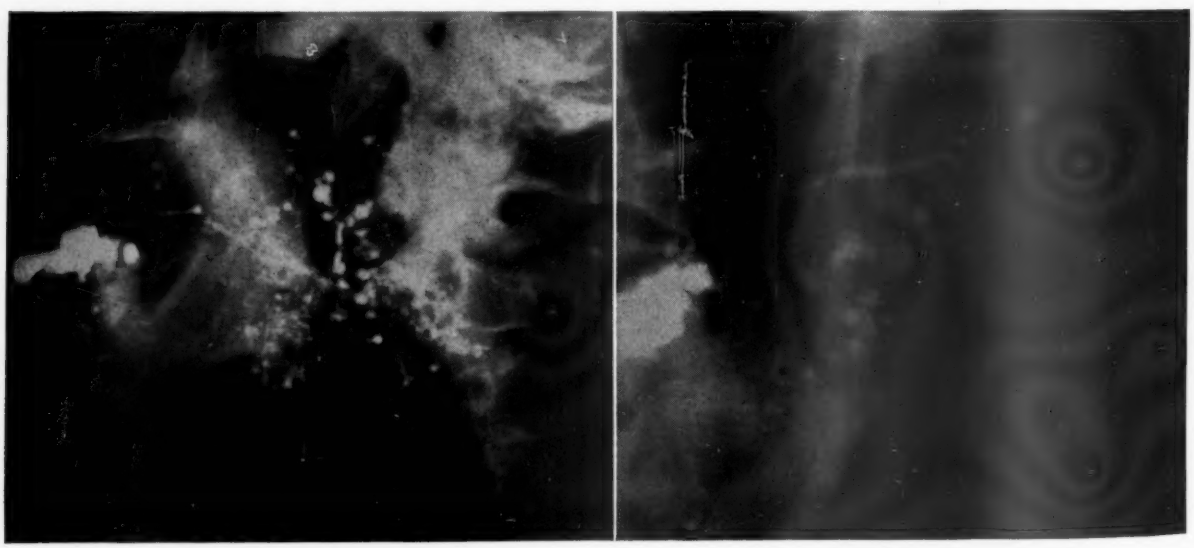

Fig. 3. Fig. 4.

Fig. 3.—Lateral view of sialogram of left parotid. Note absence of obstruction of Stenson's duct, complete filling of gland, and puddling of contrast medium.

Fig. 4.—Posteroanterior view of sialogram of left parotid. The large size of the gland with displacement of ducts and acinar elements by soft tissue mass are notable.

fully in ten weeks. The patient was readmitted on April 27, 1949, for total resection of the left parotid gland. Fourteen weeks were required for recovery from postoperative left facial nerve paralysis (see Fig. 2). There has been no enlargement of the lacrimal or remaining salivary glands on follow-up examination. The blood picture has remained normal.

Fig. 5.

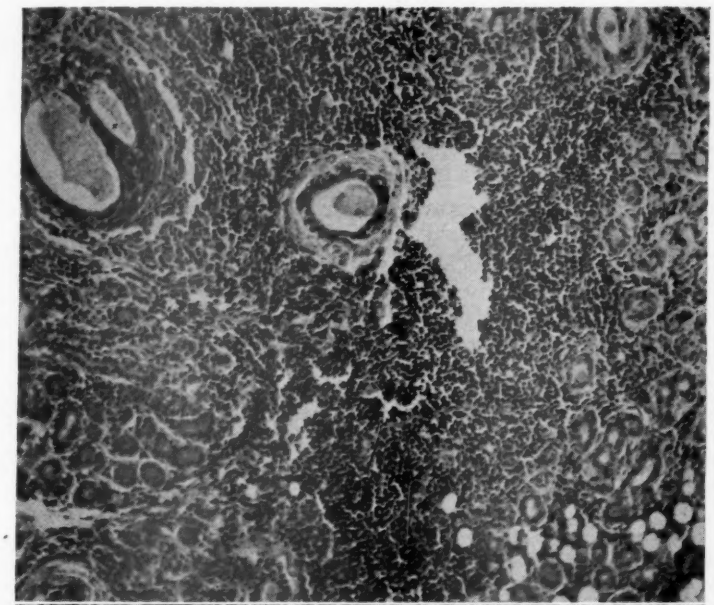

Fig. 6.

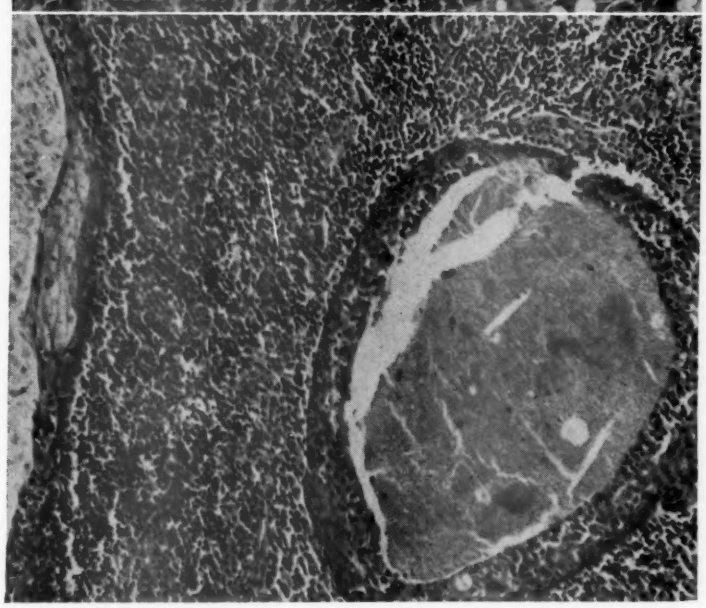

Fig. 5.—Parotid gland showing lymphocytic infiltration with early cyst formation and moderate destruction of glands (hematoxylin and eosin, ×100).

Fig. 6.—Area of more extensive destruction with cystic formation. Squamous metaplasia is present in the larger cysts (hematoxylin and eosin, ×100).

Comment.—Since Mikulicz[1] first described the entity which bears his name, numerous reports have appeared in the medical literature describing variants of this syndrome. There has been a tendency[2] to classify this group of patients into two categories, Mikulicz disease and Mikulicz syndrome. The former group presents localized enlargement of the lacrimal and salivary glands without generalized adenopathy. The latter group presents associated abnormal findings in blood, peripheral lymphadenopathy, and even involvement of distant organs such as the lungs and the stomach. A more detailed discussion and a bibliography are to be found in a recent report by Jackson.[3] Swinton and Warren[4] found seven similar lesions in their survey of eighty-one parotid tumors. All occurred in women, two of this group of seven were bilateral, and observation up to six years revealed no recurrence after surgical treatment.

SUMMARY

A case of Mikulicz's disease is presented. Total resection of both parotid glands was carried out with an excellent clinical result.

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Surgical Technique

ONE-STAGE MULTIPLE APPROACH OPERATION FOR CANCER OF THE UPPER AND MID-THORACIC ESOPHAGUS

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INTRODUCTION

THE idea of right thoracic approach to the esophagus is by no means new, as obvious anatomic advantages have long been recognized. Ivor Lewis[2] of Great Britain recommended its use in a report of his experiences with carcinoma of the esophagus in July, 1946. He employed a staged procedure, usually exploring the abdomen first for metastases. If none were found, the cardia and upper portions of the stomach were mobilized in preparation for the next stage. The approach at the second stage was through the right chest with the patient lying on the left side. The stomach could then be pulled into the right chest and resection and anastomosis carried out as with the more familiar technique on the left. In some cases he employed a preliminary cervical dissection stage but not in anticipation of an intrathoracic or cervical anastomosis. Further, he suggested that the abdominal and thoracic stages may be done consecutively at the same sitting.

Insofar as the literature is concerned, the idea was next reported upon by Macmanus[3] in this country, who published his experiences in July, 1948. He experimented with consecutive left upper abdominal and right thoracic approaches and after use on two patients found that "It was surprising to observe that the operation seemed technically less tedious, maintained its status as a cancer operation, preserved the phrenic nerve function bilaterally, did not require radical incision of the diaphragm, allowed one to transect the esophagus at any desired level and effect an anastomosis without interference by the aortic arch, resulted in less total gross trauma to the patient's tissues, and consumed less operative time." He also recommended that both stages be done on the same day whenever feasible.

Kent and Harbison[1] reported a considerably larger series of cases before the annual meeting of the American Association for Thoracic Surgery in April, 1949, at New Orleans. Their experience had been favorable but met with considerable criticism from those most accustomed to the left approach.

Using a projection of these basic ideas we have, in selected cases, utilized a one-stage procedure employing separate simultaneous cervical, thoracic, and abdominal incisions for esophagectomy and esophagogastrostomy with considerable enhancement of the procedure.

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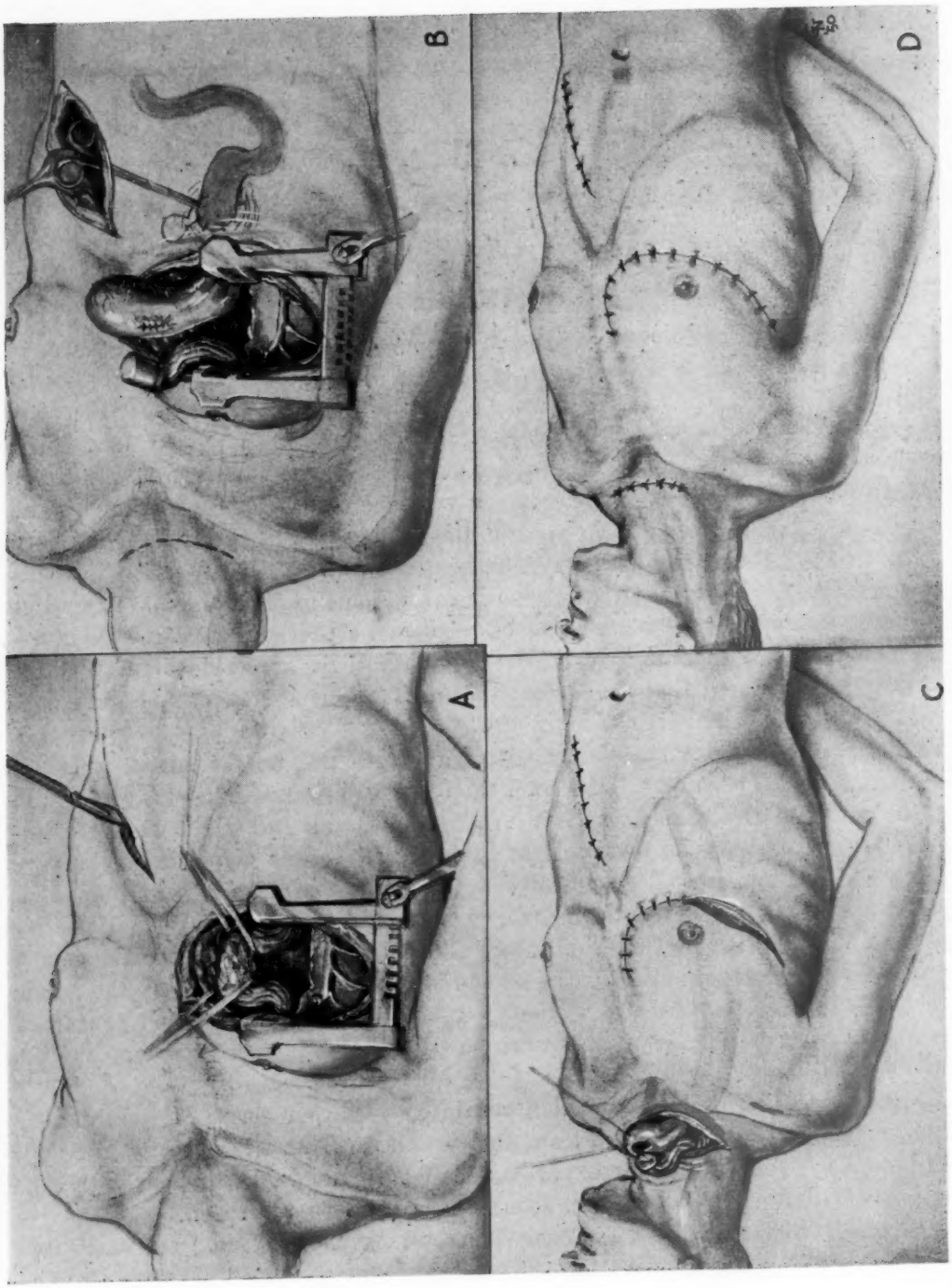

Fig. 1.—Semidiagrammatic illustration of the approach and staging of the operative procedure.

ILLUSTRATIVE TRIAL CASE REPORTS

CASE 1.—C. A., a 64-year-old Negro woman, had a history of increasing difficulty in swallowing for eight months and inability to take anything by mouth for almost four weeks. She was extremely emaciated and the red blood cell count was 3.1 million. X-ray examination showed an obstructive lesion in the mid-esophagus, which on biopsy was reported to be a squamous-cell carcinoma.

Fig. 2.

Fig. 3.

Fig. 2 (Case 2).—Preoperative esophagram showing extensive midthoracic tumor.
Fig. 3 (Case 2).—Postoperative esophagram with anastomosis slightly above clavicle.

A preliminary Stamm gastrostomy was established in order to build up her general condition, and approximately one month later an exploratory operation was performed. An anterior thoracic approach was made with the patient in a dorsal recumbent position. The tumor was found to be large, involving the azygos vein, pericardium, and fascia over the

vertebrae. By the time this could be fully ascertained it was decided that a resection was the safest and the best procedure. Accordingly, a left subcostal incision was made by an assistant. The stomach was mobilized and passed into the right chest. The antral portion of the stomach was then sutured in the esophageal hiatus, and the abdominal wound was closed. Within the chest the cardia was transected and closed. An incision was made along the border of the right sternomastoid and both the esophagus and the fundus of the stomach

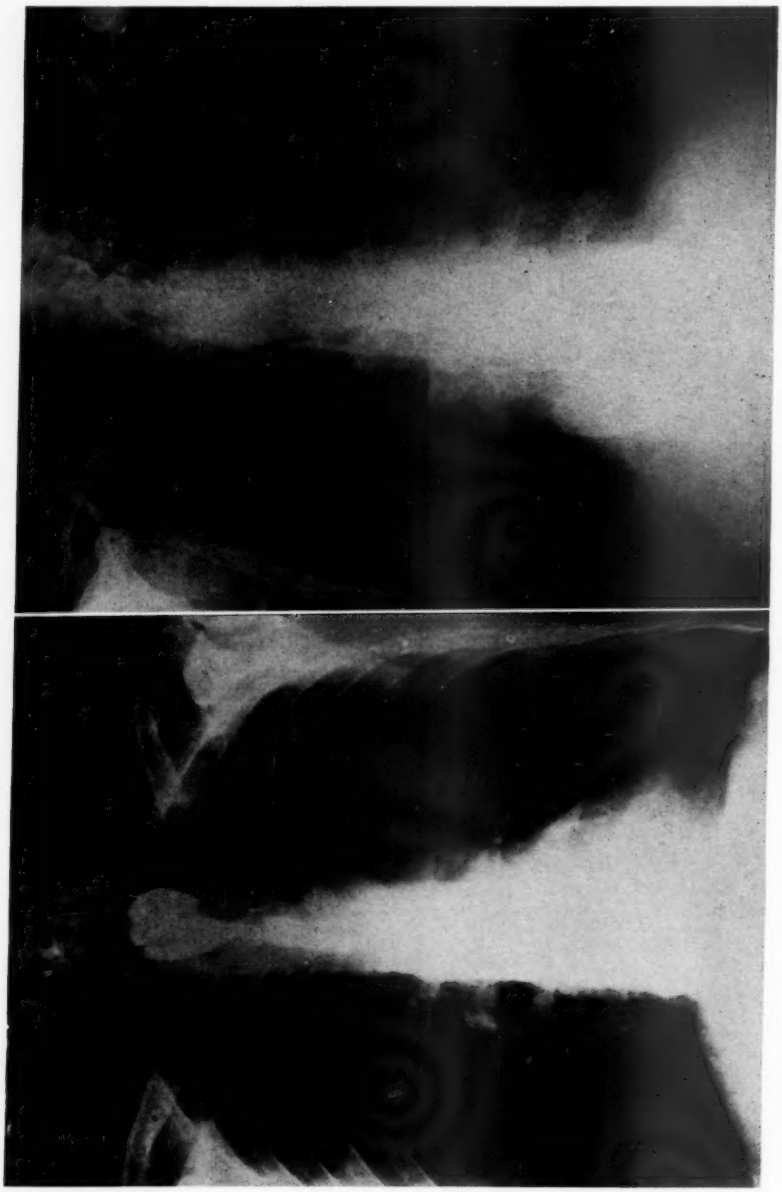

Fig. 4.

Fig. 5.

Fig. 4 (Case 3).—Preoperative esophagram showing lesion at level of suprasternal notch.
Fig. 5 (Case 3).—Postoperative esophagram showing the anastomosis at the second thoracic vertebra. This had pulled down and narrowed somewhat due to tension.

were drawn out the neck. The chest was then closed while the anastomosis was made on the neck. When the anastomosis was completed it was dropped back into the mediastinum and the neck was closed.

After operation she had gastric stasis and finally required a second abdominal operation to enlarge the esophageal hiatus. Since then she has done well and the palliative result eight months later could be considered good. The tumor was a squamous-cell carcinoma, grade 3 (Broders).

CASE 2.—K. B., a 59-year-old Negro, had increasing difficulty in swallowing for three months before admission to the hospital. He had lost only about 5 pounds and was in fairly good general condition. X-ray examination showed an extensive filling defect in the esophagus from the arch of the aorta downward at least 7 cm., which was found by biopsy to be an infiltrating squamous-cell carcinoma.

A procedure similar to the one described in the previous case was carried out. A massive tumor was found infiltrating the mediastinum but since it came away from the aorta and pericardium it was removed in spite of its attachment to the vertebrae and azygos vein. The patient made a very gratifying recovery and never had any difficulty with his eating. Within five months a right supraclavicular mass appeared which on biopsy, was found to be carcinoma, and his condition has been becoming worse rapidly, although he has no difficulty swallowing.

CASE 3.—F. B., a 61-year-old white man, was referred to the hospital with a history of increasing difficulty in swallowing of seven months' duration. He was still able to take liquids and had lost only 7 pounds of weight. There had been no pain or other difficulty. Esophragm showed an obstructing filling defect at the level of the suprasternal notch and biopsy revealed squamous-cell carcinoma.

Proper approach to this lesion seemed to indicate simultaneous cervical and thoracic incisions. When it was determined that the lesion could be resected, a left subcostal abdominal incision was made and the fundus brought on into the neck. The upper extent of the cancer was 3 cm. from the cricoid cartilage so that the esophagus was transected with a cuff of only about 1.5 cm. remaining. A two-layer anastomosis was made.

Postoperatively the patient could drink and eat well as long as he did not hyperextend the neck as in draining a glass. This blocked his swallowing. The carcinoma was grade 2 (Broders) and the prognosis seems relatively good in this case.

CASE 4.—F. J., a 67-year-old Negro, gave a history of increasing difficulty in swallowing for ten months. There had been some associated dull burning epigastric and substernal pain. Weight loss had been only 10 pounds, and he could still take some soft food slowly. He had a markedly increased erythrocyte sedimentation rate; he was mildly anemic, and serum proteins were slightly below normal. X-ray examination showed extensive involvement of the esophagus at the level of the arch of the aorta and biopsy was positive for carcinoma.

The same combination three-way approach was made and a tumor was found infiltrating the region of the left main bronchus. This stripped away, but it was apparent that considerable tumor was left behind. Even under these circumstances a palliative anastomosis seemed warranted and this was carried out by bringing the fundus out the neck wound for anastomosis.

He recovered much as would be expected from an ordinary exploratory operation so that two or three hours of extra work for the surgical team did not seem too big a price for his ability to eat in relative comfort during what life remained to him.

SYNTHESIS

It seems probable from the foregoing data that a more logical plan for surgical attack on cancer of the esophagus can be developed. For the moment we believe this to be somewhat after the following manner. For those lesions low enough that an anastomosis can be made below the arch of the aorta and for all low lesions in which extension in the region of the diaphragm is likely, the popular left thoracic approach should be used. For all lesions above that level we believe the right approach to be better and, further, that positioning of the patient so as to allow simultaneous approach through abdomen, chest, and neck offers greatest advantages both to patient and operative team.

The patient may be placed on the operating table supine with a small sandbag under the right side of the chest to tilt that side upward somewhat. A

pectoral flap can be raised and the chest entered through a widely opened third interspace. Except for the azygos vein this offers unobstructed access to the entire thoracic esophagus. Thus resectability, the most critical question, can be decided first.

As soon as that is determined the left upper abdomen can be opened and the cardia and stomach mobilized. By working from above and below, the stomach can easily be drawn into the right chest. The right diaphragmatic crus may be cut as indicated. When the extent to which the stomach is to be drawn through the diaphragm has been established, it can be fixed to the hiatus and the abdomen can then be closed by an assistant while the main train of surgery is continuing on the esophagus.

In most instances after the esophagus is resected a fairly short stump will remain in the chest. Then, because of the slope of the thoracic inlet, with little or no further dissection of the esophagus the stump can be easily drawn out through a neck incision. A suitable clamp can be passed in through the same wound and the fundus grasped and drawn out in the same way, adding little, if any, tension on the stomach for the reason mentioned previously.

An assistant can then close the chest while the esophagogastric anastomosis is progressing with relative ease on the patient's neck. When the anastomosis is completed, the esophagus can be dropped back into the mediastinum, the neck wound closed, and the operation completed. Routine measures such as drainage of the chest postoperatively are very important but a matter of individual preference. In those cases where the upper esophageal stump is long enough that anastomosis through the neck is not warranted, because of the high opening in the chest (third interspace) the anastomosis is relatively easy through the original wound.

DISCUSSION

It is significant that Macmanus should express surprise that such an operation seemed so much less tedious and technically easier. Although there has appeared no analysis of why anastomosis above the arch of aorta on the left should carry a significantly higher mortality rate, several authors have called attention to this fact. It is reasonable to assume that at least part of this may be attributable to increasing technical difficulties in higher anastomoses. Herein lies the principal recommendation for the previously outlined procedure, the lessening of strain both on the patient and on the surgeon.

The various factors enumerated are:

1. The approach to all the thoracic esophagus except the lowest part is easier and more direct.

2. The azygos vein is the only impeding structure. Many thoracic lesions involve the azygos and are difficult to handle from the left.

3. The aortic arch and the left subclavian artery act as a bolster against the left pleura during dissection. (These three factors were mentioned by Lewis.)

4. Over-all operating time is decreased due to greater ease and to overlapping of operative procedures. The abdomen may be closed while work proceeds in the chest, whereas the left chest cannot be closed until the diaphragm is

closed. The chest may be closed while the anastomosis proceeds on the neck, thereby making it less shocking for the patient and easier for the anesthetist to control the patient.

5. Greater ease and deliberativeness in performing the anastomosis result in greater safety to the patient and more saving of time.

6. The chest is open for a much shorter time.

7. Likelihood of postoperative pulmonary complications is diminished due to preservation of phrenic function (Macmanus).

8. The tendency to transect the esophagus too close to the lesion is removed since it is easier to do a high anastomosis than one in the chest.

9. The supine position probably provides a better anesthetic risk, and the patient does not have to be turned.

10. Finally, if palliation is to be considered a worth-while endeavor, there is hardly any doubt that more lesions will be considered resectable from the right because of the safer, easier approach.

Various objections might be raised and, of course, the left approach has some very definite advantages. Let it be said in the beginning, however, that the multiplicity of incisions is hardly a valid objection. The difference between opening the abdominal wall and opening the diaphragm does not admit of a great deal of argument, while the advantage of the neck incision far outweighs its objectionable features. The actual amount of tissue incised does not seem to be as important as the time saved and the other factors that have been mentioned.

The matter of preliminary abdominal exploration resolves itself into somewhat of a philosophical problem in palliation. We have felt justified in performing a resection and anastomosis for any resectable lesion without obvious clinical extension or metastasis. Every effort should be made to determine this preoperatively. Once exploration is decided upon, however, resectability becomes the first consideration. In doubtful cases the two-stage procedure may be of advantage, offering gastrostomy when metastasis are found.

The left transthoracic approach probably offers better access to the regional lymphatics, particularly just above and below the diaphragm, but probably not of a degree to be a critical point. Certainly the cardia and lowest part of the esophagus can best be approached from the left, and lesions that extend into the crura require this exposure.

In order to bring the stomach into the neck, Sweet[4] has recommended resection of the medial end of the clavicle. We have encountered no difficulty with simple incision along the medial border of the sternomastoid muscle as mentioned by Wylie[5] and others. Lewis stressed the formation of a bed of stomach wall for the esophageal stump and other measures to bolster the anastomosis. While the idea is entirely commendable, we believe that the approach is wrong. The essential element in this anastomosis is the proper and adequate coaptation of the severed structures; that is, the muscular and mucosal layers. For this reason this step is performed in such a way that the anastomosis may be rotated 180° in each direction so that the individual layers may be accurately apposed by carefully placed and controlled interrupted sutures. Since an anastomosis is only as strong as its weakest stitch, there should be no "corner," "deep," or "blind" stitch used.

We begin with a few cotton sutures on the far muscular layers to approximate the structures. The knots are on the outside and the ends are left long as markers. Next the mucosae are accurately approximated with many interrupted sutures of 0000 chromic catgut on atraumatic needles with the knots into the lumen. Then the seromuscular row is completed. The anastomosis is rotated so that the sutures on the back side are as accurately placed as those on the front. Additional rows have not been found necessary. In twenty such anastomoses not one has shown any evidence of leaking. One patient died on the ninth day of cerebral accident. The anastomosis was smooth, the mucosa was well united, and there was no swelling or obstruction. After the first case in which a routine postoperative dilatation was done we have had no further reason to carry out this practice. No patient since has required dilatation.

From study of barium esophagrams it has been our observation that the tendency of the thoracic stomach is to float upward rather than to drag on the anastomosis and this has been substantiated by two autopsies, one early and one late. Therefore, fixing the stomach to mediastinal pleura is probably important, but for the reason that it prevents kinking of the remaining esophagus due to the floating up of the stomach, rather than to prevent drag of the stomach. If there is tension on the anastomosis it is because not enough of the stomach has been brought into the chest. This is usually not difficult to overcome.

Beyond the recommendations of Macmanus and Lewis, then, we propose:

1. To eliminate turning by more or less simultaneous anterior approaches.
2. To shorten further operating time by overlapping the various stages.
3. To incorporate the cervical anastomosis in most of the higher lesions to ease the strain both on patient and surgeon.

SUMMARY

We have here endeavored to analyze some of the technical factors pertaining to surgical treatment of carcinoma of the esophagus and draw certain conclusions therefrom. Recommendations for a more varied approach dictated by circumstances have been made. Observations on a small number of cases have appeared to be well enough controlled to indicate significant advantages to an approach through separate incisions into the abdomen, right chest, and neck at more or less the same time.

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Editorial

The Procrustean Bed and the Management of Bleeding Peptic Ulcer

IN MEDICAL discussions, written and spoken, one can detect a yearning for standardization, which, though easy to understand, is not necessarily commendable. This is much more evident in respect to the treatment of the patient than in the use of diagnostic and analytical methods of studying his disease. Since the surgeon is more likely to be preoccupied with treatment than is the internist, the tendency noted is perhaps more prevalent among surgeons. Obviously it cannot be assumed that similar lesions should be handled in the same way by all surgeons, any more than it can be assumed that all surgeons have equal means and skill. Such assumptions in their *reductio ad absurdum* would hold that a surgical operation for any given lesion is an invariable commodity, like some item of commerce.

This Procrustean fallacy seems to color some of the current discussions of the management of bleeding peptic ulcer. Clearly the treatment of choice in each instance is that which yields the best early and late results, but there is no reason to suppose that this will be the same in every clinic.

There is mounting evidence that a patient with exsanguinating duodenal or gastric ulcer can be successfully treated by immediate restoration of hemoglobin values and surgical prevention of further bleeding. The requisite surgical procedure is subtotal gastrectomy, which happens to be at the same time the most effective means of assuring the patient freedom from recurrence of ulcer. This method has recently been applied to forty consecutive patients seriously exsanguinated and with total circulating red cell mass less than 60 per cent of normal. One of the patients was 80 years old, and the incidence of associated disease in the group was high. There were two deaths. A 75-year-old man was admitted with severe cerebral anoxia, convulsions, and a total circulating red cell mass of only 18 per cent, and died of bronchopneumonia and uremia eleven days after operation. A 60-year-old woman who was admitted to the hospital after nine days of hematemesis and melena with a total circulating red cell mass of 23 per cent died three days after operation.

It should be pointed out at once that this method is not being recommended for general adoption. Necessary to its success are resident and laboratory teams available round the clock and eagerly interested in the program. A blood bank with large and fluid assets, anesthesia facilities of high order, and considerable experience in difficult gastric surgery are further requisites. A willingness to work at night and to sacrifice the day's routine also should be mentioned among the essentials.

The question might be raised as to how a clinic is to determine what its best method for treating bleeding peptic ulcer is. The answer does not seem obscure. It is a matter of setting up methods of study which will permit the test group to be identified and appraised accurately, choosing criteria to be observed in the series, and then applying the different methods of treatment in alternation. As the series increases in size, the uncontrollable variables have less and less significance and any advantage of one method over another stands out. In using this approach to the problem in the study referred to previously it was not long before the superiority of the surgical over the nonsurgical treatment was apparent.

In the promotion of orthodoxy it is adherence to right teaching rather than conformity to pattern which is our goal. Right teaching would seem to enjoin the surgeon to weigh his own equipment as well as the problem presented to him by his patient.

—John D. Stewart, M.D.